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ASSESSMENT OF LIQUID SILOXANES (SILICONES)

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SEPTEMBER 1974

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ASSESSMENT OF LIQUID SILOXANES (SILICONES)

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SEPTEMBER 1975

FINAL REPORT

PRICES SUBJECT TO CHANGE

OFFICE OF TOXIC SUBSTANCES
U.S. ENVIRONMENT PROTECTION AGENCY
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16. ABSTRACT

This report reviews the potential environmental hazard from the commercial use of large quantities of liquid siloxanes which are used for the most part in waxes, polishes, cosmetics, and in the foaming of polyurethane; and as lubricants, antifoaming agents, release agents, and protective coatings for textiles, glass and leather. Polydimethylsiloxane and polymethylphenylsiloxane were of major interest as commercial products, although low molecular weight siloxanes were also reviewed. Information is presented on the chemical properties, production methods, quantities produced and released, commercial uses and factors affecting environmental contamination as well as data on health and biological effects.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Siloxanes, silicones, organic silicon compounds, polydimethylsiloxane, polymethylphenylsiloxane, antifoams, toxicology, chemical properties, pollution, production, utilization.	Pollution Environmental exposure Environmental effects	

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LIQUID SILOXANES (SILICONES)

This review assesses the potential environmental hazard from the commercial use of silicone fluids. These have been broadly defined as any commercial composition which contains the siloxane polymer chain ($[-\overset{R}{\underset{R}{Si}}-O-]_x$) and has a measurable viscosity. A broader review of environmental hazard from the commercial use of silicone fluids, elastomers, and resins has previously been reported (Howard and Durkin, 1973).

Organosilicon chemistry gained a foundation through the classical studies of Kipping during 1900-1940 (see Lichtenwalner & Sprung, 1970). Kipping used the term "silicone" in expectation that the organosilicon compounds would form compounds analogous to the ketones of organic chemistry, in which the carbon of the carbonyl group would be replaced by a silicon atom (Hyde, 1965). However, the organosilicon compounds did not form silicon-oxygen double bonds, but instead they condensed to higher molecular-weight siloxane (Si-O-Si) compounds. Nevertheless the term silicones has remained and is generally applied to "polymeric siloxane products, usually complex, often undefinable in exact scientific terms, frequently mixtures of many components, and in many cases useful in one or more practical ways" (Litchtenwalner & Sprung, 1970, p. 466).

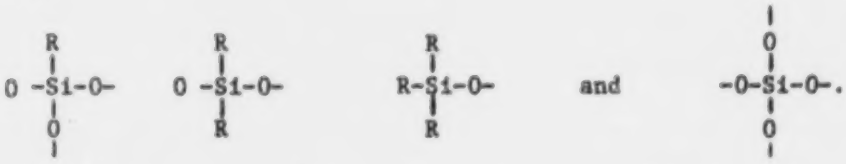
Silicones became commercially important after a large development effort by Hyde, Sullivan, and associates of the Corning Glass Company, McGregor and associates of the Mellon Institute, and Rochow, Patnode, Marshall and associates of the General Electric Company. The first silicones operation was established in 1943 as a joint program between the Corning Glass Works,

the Corning Fellowship at Mellon Institute, and the Dow Chemical Company. Today, hundreds of silicone products are manufactured throughout the world and find uses in virtually every industry.

I. Structure and Properties

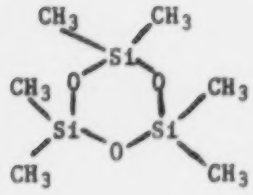
A. Chemical Structure

Silicon, like carbon, forms four sigma bonds to other atoms and maintains a tetrahedral configuration. Silicones must have at least one siloxane chain (-Si-O-Si-), and, therefore, the silicones can be composed of four types of units:

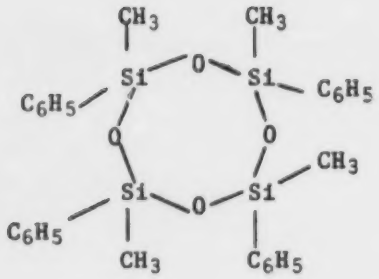


Various combinations of these four units can result in such compounds as the following:

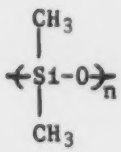
Table I. Structure and Nomenclature of Several Silicone Compounds



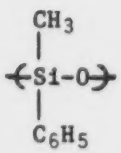
hexamethylcyclotrisiloxane



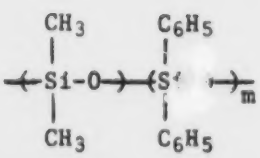
1,3,5,7-tetramethyl-1,3,5,7-tetraphenylcyclotetrasiloxane



poly(dimethylsiloxane)



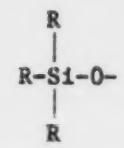
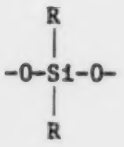
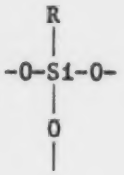
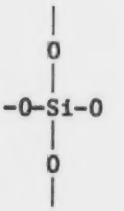
poly(methylphenylsiloxane)



Poly(dimethylsiloxane-co-diphenylsiloxane)

As can be seen from Table I, the siloxane nomenclature becomes very cumbersome and, therefore, the industry has adopted a convenient shorthand which identifies the four types of units by letters, as depicted in Table II.

Table II. Shorthand Letter Designations for Silicone Compounds

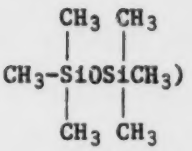
	R = CH_3-	R ≠ CH_3-
	M	M'
	D	D'
	T	T'
	Q	Q

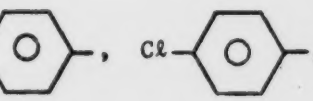
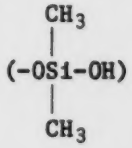
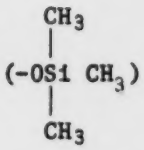
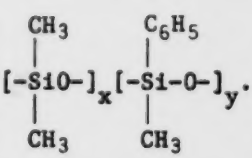
Examples:

$(CH_3)_3SiOSi(CH_3)_3$ M_2

$(CH_3)\ Si\text{-}O[Si(CH_3)_2O]_2Si(CH_3)_3$ MD_2M

The commercial silicones are extremely complex polymer mixtures. The fluids normally consists of long, straight-chain polydimethylsiloxanes (MD_xM) which can vary in molecular weight from 162 for the dimer (hexamethyldisiloxane-



to molecular weights of several hundred thousand. Organic substituents, such as ,  , CH_3CH_2-, $CH_2=CH_2-$, $CH_3CH_2CH_2-$, $CF_3CH_2CH_2-$ and H-, can also form covalent bonds with the silicon, and provide such mixtures as polymethylphenyl-, polydiphenyl-, and polymethylvinylsiloxanes. The fluids may have an open end  but more frequently they are terminated with M units  In many cases, a mixture of organic substituents is used to form a copolymer which possesses the appropriate physical properties. For example, a common fluid is polydimethylsiloxane with a small percentage of methylphenyl substituted groups evenly distributed throughout the polymer chain  . In contrast to the straight chain fluids, the elastomers and resins contain T and Q groups or reactive organic side chains (e.g. vinyl) which allow crosslinking of the polymers resulting in a more rigid matrix.

The low molecular-weight oligomeric polysiloxanes have definite molecular weights and can be isolated by distillation or crystallization. However, once the number of difunctional units (D) reaches 10, identification of individual compounds is no longer possible. The number of difunctional groups may continue to at least 10,000 D units (Noll, 1968, p 249). Since the commercial polysiloxane fluids consist mostly of high molecular weight formulations, they are made up of a broad molecular size distribution. Because of this lack of sharply defined molecular size, the practice of referring to the fluids in terms of viscosity has arisen. Since the viscosity correlates to some degree with the mean molecular weight (Noll, 1968, p. 250) as can be seen in Table III, the viscosity roughly corresponds to the degree of polymerization.

Table III. Viscosity and Calculated Weight-Average Molecular Weights ($\bar{M}$) and Average Number of Siloxane Units ($\bar{N}$) per Molecule in a Series of Linear Polydimethylsiloxanes (Noll, 1968, p 253)

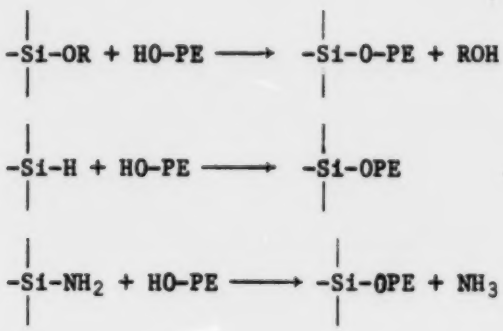
ν_{20}[cSt]	$\bar{M}$	$\bar{N}$
60	3600	50
140	8000	110
440	17000	230
680	21000	280
1440	30000	400
10000	60000	800
50000	88000	1200
100000	103000	1400
300000	143000	1900

The siloxane polymer chain can also be connected to non-siloxane polymers to form copolymers. Commercially one of the most important of

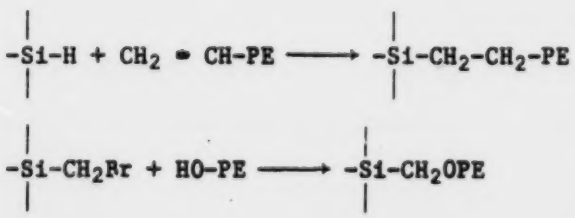
these combined polymers is the silicone-polyoxyalkylene (also referred to as silicone polyether copolymers or silicone glycols) block block copolymers. The block block refers to the fact that these copolymers consist of a block of siloxane polymers attached to a block of polyether (PE) polymer. These copolymers can be divided into two large groups, (1) those with Si-O-C bonds, and (2) those with Si-C bonds. Table IV illustrates some of the synthesis routes used.

Table IV. Synthesis of Silicone-polyether (PE) Copolymers

Si-O-C Bridges

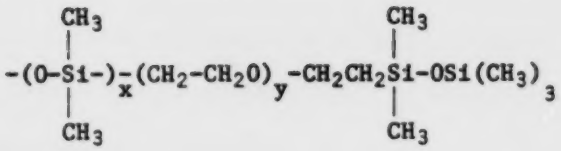


Si-C Bridges

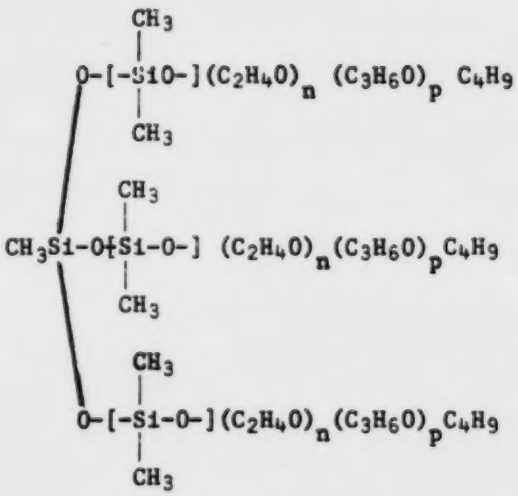


The polyether most frequently consists of ethylene oxide and propylene oxide units, and the copolymer may be linear (I) or branched (II) (Noll, 1968).

(I)



(II)



B. Physical Properties of the Pure Materials

Only the low molecular weight cyclic and linear siloxanes have been isolated and characterized in pure form. The physical properties of the volatile dimethylsilicone oligomers are presented in Table V.

Table V. Physical Properties of Low Molecular Weight Dimethyl Silicones (Meals, 1969, p. 226)

Symbol	Melting point, °C	Boiling point, °C	Density, d^{20}	Refractive Index, n_D^{20}	Viscosity, n, at 25°C, cSt.	Flash point, °F
MM	-67	99.5	0.7636	1.3774	0.65	15
MDM	-80	153	0.8200	1.3840	1.04	98
MD_2M	-76	194	0.8536	1.3895	1.53	158
MD_3M	-80	229	0.8755	1.3925	2.06	202
MD_4M	-59	245	0.8910	1.3948	2.63	245
MD_5M	-78	270	0.9012	1.3965	3.24	272
MD_6M	-63	290	0.9099	1.3970	3.88	292
MD_7M		307.5	0.9180	1.3980	4.58	318
D_3 (cyclic)	64.5	134				
D_4	17.5	175.8	0.9561	1.3968	2.30	156
D_5	-44	210	0.9593	1.3982	3.87	
D_6	-3	245	0.9672	1.4015	6.62	
D_7	-32	154[a]	0.9730	1.4040	9.47	
D_8	31.5	290	1.1770[b]	1.4060	13.23	

[a]At 20 mm Hg. [b]Crystals.

C. Physical Properties of Commercial Materials

The higher viscosity polydimethylsiloxanes and polymethylphenylsiloxanes, which make up the bulk of the technical products, have the following characteristic properties: "heat resistance; low-temperature resistance; resistance to weather, ozone, and corona discharge; low variability of the physical constants with temperature; good dielectric properties; film-forming ability; hydrophobic behavior; release action; surface activity; and physiological inertness" (Noll, 1968, p 437). These properties are intimately related to the commercial application of the compounds. This section will discuss the physical properties; chemical properties will be discussed in Section VIII; and physiological properties will be discussed in Sections XI-XV.

Table VI presents some general physical properties of a number of silicone fluids sold by Dow Corning. A more detailed discussion of the physical properties is presented in the following paragraphs.

Many of the commercial applications of silicone fluids are due to their ability to function at extreme temperatures (both high and low). The low variation of the viscosity of methylsilicone oils with temperature provides a striking illustration of that property, as is shown in Figure 1. However, replacement of the methyl groups by other groups tends to increase the temperature dependence of the viscosity.

Pressure has only a slight effect on the viscosity. For example, a pressure of 2000 atmospheres increases the viscosity of mineral oil by a factor of about 50-500, but silicone oil (140 cSt.) viscosity is increased by only a factor of 16 (Noll, 1968). Furthermore, for liquid siloxanes of up to 1000 cSt., shear forces have little effect.

Table VI. Typical Physical Properties of Dow Corning Silicone Fluids (Dow Corning, 1972a)

Fluid #	Type	Viscosity cSt.	Flash Point Open Cup °C	Pour Point °C	Specific Gravity (25°C)	Coefficient of Expansion cc/cc°C	Surface Tension at 23°C dyne/cm	Thermal Conductivity at 25°C cal/sec-cm°C	Volatility % at Temp.	Refractive Index	Dielectric Constant 100 H_2 25°C	150°C
200	Dimethyl	5.0	135	-65	0.920	0.00105	19.7	0.00028	-----	1.397	2.59	2.24
		10	165	-65	0.940	0.00108	20.1	0.00032	-----	1.399	2.64	2.28
		20	230	-60	0.955	0.00107	20.6	0.00034	-----	1.400	2.68	2.32
		50	280	-55	0.960	0.00104	20.8	0.00036	150, 2.0%	1.402	2.71	2.35
		100	300	-55	0.968	0.00096	20.9	0.00037	150, <0.5%	1.403	2.73	2.37
		200	315	-52	0.971	0.00096	21.0	0.00037	150, <0.5%	1.4031	2.74	2.38
		350	315	-50	0.972	0.00096	21.1	0.00038	150, <0.5%	1.4032	2.75	2.39
		500	315	-50	0.972	0.00096	21.1	0.00038	150, <0.5%	1.4033	2.75	2.39
		1,000	315	-50	0.972	0.00096	21.2	0.00038	150, <0.5%	1.4035	2.77	2.41
		12,500	315	-46	0.973	0.00096	21.5	0.00038	150, <2%	1.4035	2.77	2.41
		30,000	315	-44	0.973	0.00096	21.5	0.00038	150, <2%	1.4035	2.77	2.41
		60,000	315	-41	0.973	0.00096	21.5	0.00038	150, <2%	1.4035	2.77	2.41
203		1,200	232	--	0.91	--	--	---	---	1.464	--	--
230		1,400	204	--	1.009	--	--	---	--	1.462	2.74	--
330	Branched Dimethyl	50	279	-73	0.97	0.00107	20.5	0.00034	200, 2.0%	1.4025	2.72	--
510	Phenylmethyl	50	275	-73	1.00	0.00096	25.0	0.00035	200, 2.0%	1.425	2.77	2.42
		100	275	-73	1.00	0.00096	24.1	0.00036	200, 1.5%	1.425	2.78	2.44
		500	275	-73	1.00	0.00096	24.4	0.00037	200, 1.5%	1.425	2.80	2.46
550	Phenyl-methyl	125	300	-51	1.07	0.00075	24.5	0.00035	250, 9%	1.50	2.90	2.57
560	Chlorophenyl-methyl	75	288	-65	1.040	0.00095	22.7	--	---	1.434	--	--
710	Phenyl-methyl	500	300	-20	1.11	0.00077	28.5	0.00035	250, 9%	1.533	2.95	2.65
FS 1265	Fluoro-silicone	300	260	-47	1.25	0.00095	25.7	--	200, 10%	1.381	6.95	--
		1,000	290	-40	1.28	0.00095	26.1	--	200, 3.0%	1.382	7.35	--
		10,000	315	-30	1.30	0.00095	28.7	--	200, 1.5%	1.383	7.35	--

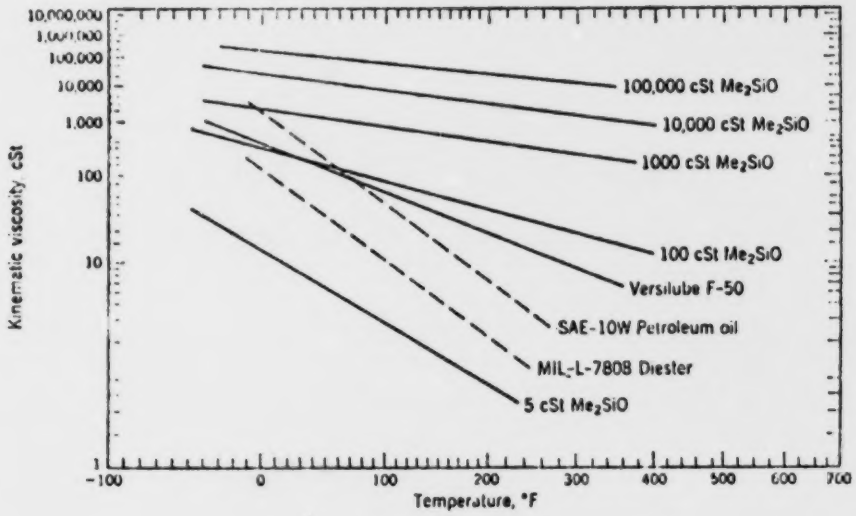


Figure 1

Viscosity-Temperature Curves for
Various Silicones (Meals, 1969);
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The vapor pressure of the commercial silicone fluids, with the exception of the lower members, is generally very low. This can be attributed to the recycling of the volatile siloxanes by distillation during manufacture of the higher polymeric siloxanes. However, even the high polymer fluids have measurable vapor pressures at elevated temperatures, as illustrated in Table VII.

Table VII. Vapor Pressures of Silicone Fluids (Noll, 1968)

cSt (20°C)	Vapor Pressure (mm Hg)
140 (dimethyl)	$<10^{-5}$(140°C); 1×10^{-4}(170°C); 8×10^{-4}(200°C)
200–1000 (methylphenyl)	10^{-6}(20°C); 10^{-5}(100°C); 10^{-4}(150°C)
30,000 (methyl)	5×10^{-5}(100°C); 3×10^{-4}(220°C)

The surface tension of all liquid silicones is surprisingly low (see Table VI) and can be attributed to the low strength of the intermolecular binding forces between polymer chains. This low strength of the intermolecular binding forces also results in a high film-forming ability. Films of molecular dimensions can be rapidly formed on both solids and liquids. Such films can reduce adhesion to sticky materials and impart water repellancy to the surfaces that are coated. These properties are "an expression of a fundamental chemical characteristic of the polymeric organosiloxane skeleton: its paraffin nature, the saturated character of the molecules, and the corresponding smallness of Van der Waals forces which permit the appearance of only slight, if any, affinity for substances of different nature"(Noll, 1968, p 452).

The compressibility of the liquid polysiloxanes is comparatively high. This results in their application as liquid springs, shock absorbers, and damping devices. The high compressibility is a result of the unusual flexibility of the molecule, leading to loose coiled configurations (helical) with a large amount of internal free space. This free space allows compression to occur relatively easily.

The dielectric properties are characterized as good in terms of dielectric constant, loss factor, specific resistance, and dielectric strength and vary only slightly with temperature (Noll, 1968).

The lubricating properties of silicone oils are generally poor. The load-bearing properties of the methyl siloxane films are especially low because of the weak intermolecular forces. Improved lubricating properties are obtained by incorporation of phenyl groups (especially halogenated phenyl groups)

and long chain alkyl groups. Recently, the $CF_3CH_2CH_2$- group has also been incorporated in siloxanes in order to increase the load bearing capacity.

The silicones also display surface active properties which result in their use as foaming and antifoaming agents. The foaming action can be attributed to the lowering of the surface tension by the siloxane. The antifoaming activity results from effects on bubble elasticity at low siloxane concentration (see Noll, 1968, p 454).

Dimethylsilicone and phenylmethylsilicone are soluble in many solvents, but their solubility is dependent to some extent on viscosity, molecular weight, and organic substitution. Good solvents include hydrocarbons (gasoline, benzene, toluene), chlorinated hydrocarbons (chloroform, carbon tetrachloride, trichloroethylene), ethers, esters, and higher alcohols from butanol onward. The lower viscosity (60-140 cSt) dimethylsilicones dissolve in isopropanol, n-propanol, n-butanol, acetone, and dioxane. The low molecular weight (5, 10, and 25 cSt) methylphenylsilicone oils dissolve in methanol and, unlike the other types of oils, are compatible with paraffins, most vegetable oils and petroleum jellies (Noll, 1968). The fluorosilicone fluids are only soluble in ketones and low molecular weight esters (Dow Corning, 1972a).

D. Principal Contaminants in Commercial Products

The silicone fluids are formed by the hydrolysis of organochlorosilanes (see Section IId). These compounds are highly purified (93-98%) by distillation and the most frequently used, dichlorodimethylsilane (used to synthesize the polydimethylsiloxane fluids), is available in purities above 99.5% (Meals, 1969).

The hexamethyldisiloxane can be purified by distillation to remove impurities resulting from hydrocarbons, $SiCl_4$, and other chlorosilanes in commercial Me_3SiCl. Thus, when the dimethylsilicone fluids are made by reacting (equilibration process) the dimethyl silicone stock (hydrolysis product of $(CH_3)_2SiCl_2$) with hexamethyldisiloxane, the result is a mixture of many siloxane isomers relatively free of non-siloxane contaminants. For the more viscous fluids, this equilibration reaction is followed by a devolatilization process which removes the light ends (cyclic and low molecular weight siloxanes) for recycling. In some instances, these light siloxanes could be considered to be impurities, but they are probably mostly removed by the devolatilization process which consists of heating in vacuum.

II. PRODUCTION

A. Quantity Produced

Details on plant capacities are not available and total production figures lack precision due to the fact that many manufacturers fail to differentiate between finished products, which contain water and solvent, and 100% silicone material. The diversity of the applications also contributes to the lack of precise information.

An estimate for 1965 placed the total production of silicones (fluids and silicone content of resins and elastomers) at about 25 million lbs. (Anon., 1965). In 1971, elastomers and resins only totaled approximately 40 million lbs. (U.S. Tariff Commission, 1972). However, it is unclear how

much of the 40 million lbs. is 100% silicone material (e.g. silicone-alkyd resins contain as little as 15% silicones). Union Carbide (Bailey, 1973) has suggested that the total market (including water in silicone emulsions and solvents in resin solutions) is approximately 200-300 million lbs. Table VIII presents some estimates of the silicone market provided by the Dow Corning Corporation (1973). The total silicone market is estimated to be 91 million lbs. with approximately 30 million lbs. of 100% silicone fluids and 18 million lbs. of silicone glycol fluids (~30% siloxane content). This is comparable to the estimate of Lewis (1967) that 45% of the total silicone production goes into silicone fluids.

Table VIII. Estimated Silicone* Usage in U.S. Market - 1973
(Dow Corning Corporation, 1973)

	10^6 lbs.*	% of total
Methyl Siloxanes (fluids (~50% of total), compounds, rubber, sealants)		
Dimethyl siloxanes	30	33
Methyl and small quantities of phenyl, vinyl, chlorophenyl, etc.	30	33
Silicone Glycols (used with polyurethanes)	18	20
Chemicals	3	3
Miscellaneous (resins, resin intermediates, fluorosilicones)	10	11
Total	91	100

*Represents silicone content except for silicone glycols. Approximately 30% of the silicone glycol figure represents siloxane compound.

B. Producers, Major Distributors, and Importers

In the United States there are four major manufacturers of silicones: Dow Corning Corporation, General Electric Company, Union Carbide Corporation, and Stauffer Chemical Company. Dow Corning is the largest producer (approximately ½ the total); General Electric produces somewhat less; Union Carbide production amounts to about 15-25% of the total (Bailey, 1973); and Stauffer is the smallest producer, with about 5% of the market.

Outside the United States, silicone producers include: Imperial Chemical Industries and Midland Silicones (United Kingdom), Société des Usines Chemiques Rhône-Poulenc and Société Industrielle des Silicones et des Produits Chemiques du Silicium (France), Union Chimique Belge (Belgium), Farbenfabriken Bayer, Wacker-Chemie, and Theo. Goldschmidt (West Germany), V.E.B. Siliconchemie and VF-V Chemie-Werk (East Germany), Societa Italiana Derivati Silicio (Italy), and Shin-etsu Company, Tokyo Shibaura Company, and Japan Silicone Company (Japan). There are also manufacturing plants in several locations in the USSR and in Czechoslovakia, as well as in Australia, and probably some in Mainland China (Lichtenwalner and Sprung, 1970).

Since silicones are in most cases a speciality commodity, there are no major distributors. However, in some cases, like with electronic fluids, authorized distributors are utilized.

C. Production Sites

Table IX lists the producer, the type of product made, and the site of the manufacturing plant. Capacities of individual plants are not available, but the total capacity in 1967 was estimated at 50 million lbs. (Lewis, 1967).

Table IX. Sites of Production of Silicone Manufacturers (Lewis, 1967)

Company	Product Type	Location
Dow Corning Corporation	Fluids, resins, elastomers	Midland, Michigan
	Dimethyl silicones ($15 x 10^6 plant)	Carrollton, Kentucky
	Silicone Sealants	Elizabethtown, Ky.
	Medical-grade Silicones	Hemlock, Michigan
	Silicone Rubber	Trumbull, Conn.
General Electric	Fluids, resins, elastomers	Waterford, N.Y.
	Silicone resins	Coshocton, Ohio
Union Carbide	Fluids, resins, elastomers	Sistersville, W. Va.
Stauffer Chemical Co.	Fluids, elastomers	Adrian, Michigan
	Elastomers	Matawan, N.J.

D. Production Methods (Gutoff, 1957; Forbath, 1957; Weaver and O'Connors, 1958; and Lichtenwalner and Sprung, 1970).

The silicone fluids are synthesized from the hydrolysis products of organochlorosilanes. The organochlorosilanes can be produced by a number of different routes, as demonstrated in Figure 2.

A $2CH_3Cl + Si \longrightarrow (CH_3)_2SiCl_2$

B $C_6H_5MgCl + SiCl_4 \longrightarrow C_6H_5SiCl_3 + MgCl_2$

C $C_6H_5MgCl + CH_3SiCl_3 \longrightarrow C_6H_5(CH_3)SiCl_2 + MgCl_2$

D $RCH = CH_2 + HSiCl_3 \longrightarrow R\,CH_2CH_2SiCl_3$

E $HC{\equiv}CH + HSiCl_3 \longrightarrow CH_2 = CHSiCl_3$

F $CH_3Cl + HCl + Si \longrightarrow CH_3HSiCl_2$

Figure 2. Synthesis of Organochlorosilanes

Reaction A in Figure 2 is the most important commercially and is commonly referred to as the "direct process". The process is used mostly for the production of methylchlorosilanes and sometimes for the phenylchlorosilanes.

Reactions B and C are Grignard processes which commercially are important in the production of methylphenylchlorosilanes. Reaction D is termed the olefin process. It is used to synthesize alkylchlorosilanes (e.g., $CF_3CH_2CH_2$-).

The direct process, which is used to produce methylchlorosilanes, consists of reacting metallic Si with methylchloride using a copper catalyst. The silicone metal is prepared by reacting coke and silica in an electric furnace.

$$CH_3Cl + Si \xrightarrow[300°C]{Cu} (CH_3)_2SiCl_2,\ (CH_3)_3SiCl,\ CH_3SiCl_3$$

The mixture of chloromethylsilanes resulting from the direct process typically falls in the general range given below (Lichtenwalner and Sprung, 1970)

$(CH_3)_2SiCl_2$	>50%
CH_3SiCl_3	10-30%
CH_3SiHCl_2	<10%
$(CH_3)_3SiCl$	<5%
other monosilanes	∿5%
higher-boiling residue	up to 10%

The chloromethylsilanes are isolated from each other by distillation. The most important commercial compound, dimethyldichlorosilane, can routinely be prepared in high purity (99.9%) by using more than 100 actual plates in the distillation (CH_3SiCl_3 boils only 4° lower). A representative flow diagram is presented in Figure 3.

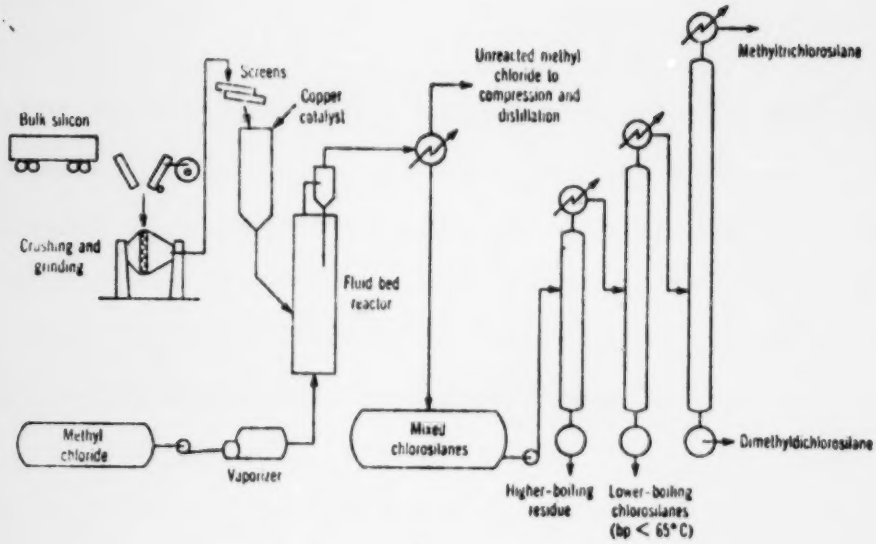

Figure 3. Flow Diagram for Dimethyldichlorosilane Production (Lichtenwalner and Sprung, 1970)
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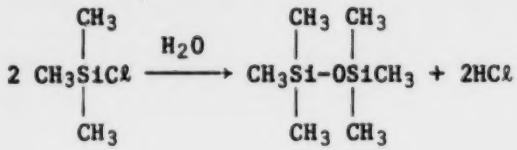
A crude mixture of straight chain and cyclic siloxanes is formed by the hydrolysis of the difunctional chlorosilanes. This is illustrated for $(CH_3)_2SiCl_2$ in the equation below:

$$(CH_3)_2SiCl_2 + H_2O \longrightarrow \underset{\text{cyclic}}{[(CH_3)_2Si)]_n} + \underset{\text{straight chain}}{HO[(CH_3)_2SiO]_m H} + HCl$$

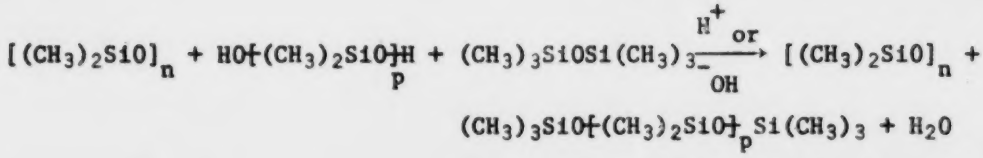
The proportion of cyclic material can vary from 20-80% depending upon the conditions. The siloxanes are decanted, washed with water or neutralizing bicarbonate solution, and dried. The hydrolysis step is typically run in glass, glass-lined steel, or plastic of suitable chemical and thermal resistance. Both batch and continuous operations (commonly used with the dimethylsilicones) are possible.

The next step to the silicone fluid product involves the equilibration of the crude siloxane mixture with either acid or base catalyst in the presence of a chain stopper (an M group such as $\begin{matrix} CH_3 \\ | \\ CH_3Si- \\ | \\ CH_3 \end{matrix}$). Normally the chain stopper

is added in the form of a disiloxane which has previously been hydrolyzed



$$2\ CH_3SiCl(CH_3)_2 \xrightarrow{H_2O} CH_3Si(CH_3)_2OSi(CH_3)_2CH_3 + 2HCl$$



$$[(CH_3)_2SiO]_n + HO\text{-}(CH_3)_2SiO\text{-}_pH + (CH_3)_3SiOSi(CH_3)_3 \xrightarrow[OH^-]{H^+ \text{ or}} [(CH_3)_2SiO]_n +$$

$$(CH_3)_3SiO\text{-}(CH_3)_2SiO\text{-}_pSi(CH_3)_3 + H_2O$$

The proportion of chain stopper to difunctional siloxane will determine the molecular distribution of the linear chains in the fluid as illustrated in Figure 4.

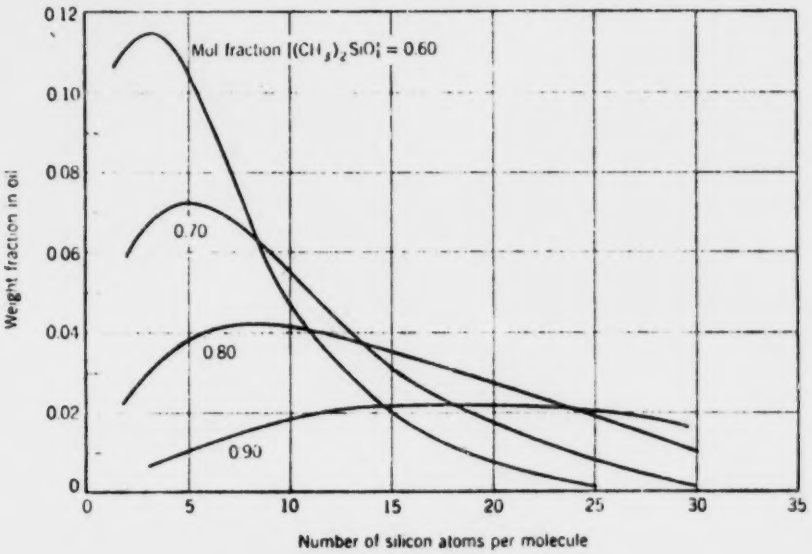


Figure 4. Molecular Distribution of Linear Dimethylsiloxane after Equilibration with Chain Stopper (Lichtenwalner and Sprung, 1970, p 524) reprinted by permission, Copyright 1970, J. Wiley & Sons

The fluid is then washed with water, neutralized, and dried by passing through an absorbent medium. The final step to the finished product involves devolatizing the fluid which removes most remaining cyclic siloxanes and low-molecular straight chains. This step yields a somewhat higher viscosity fluid.

E. Market Price

The market price of the fluids varies considerably depending upon the grade and organic substitutents used. For example, prices can be as low as under $2/lb for some dimethylsilicone fluids in drum lots to over $50/lb for specialty items (Lewis, 1967). The general price trend for the dimethyl-silicone fluids has been downward as illustrated in Figure 5.

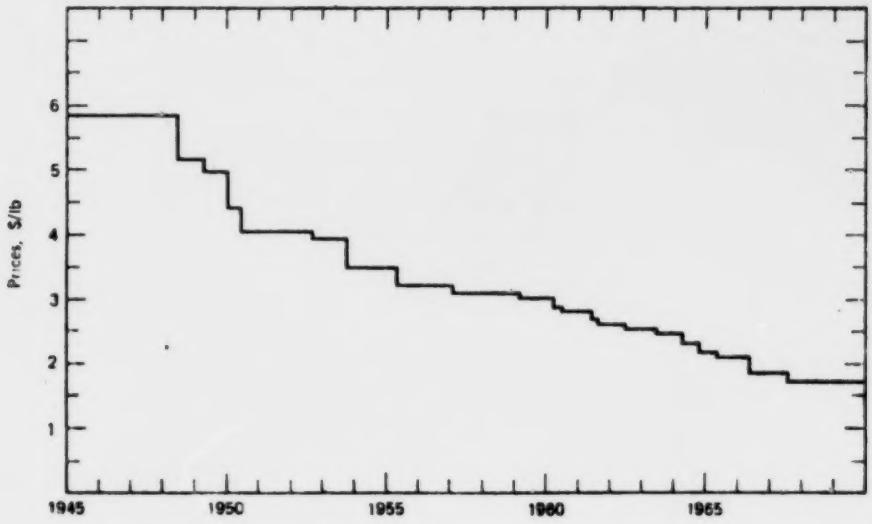


Figure 5. Price History of Dimethyl Silicone Oil
(Lichtenwalner and Sprung, 1970, p 471)
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III. Uses

A. Major Uses

The silicone fluids are used commercially for literally hundreds of applications due to the flexibility allowed by the various synthesis routes and formulation techniques. Applications resulting from both their bulk properties (thermal and oxidative stability, electric properties, and viscosity/temperature characteristics) and from their surface properties (water repellency, low surface tension, and release properties) are important. Early applications of the fluids included coolants in pumps, transformers, and other mechanical and electric equipment, and as dielectric fluids. However, because the silicone fluids are relatively expensive, their major commercial applications today employ their surface characteristics since only small amounts of material are required. These applications include polishes for automobiles, furniture, and major appliances, use as release agents, as antifoam agents, as foaming agents for polymers, and for paper and textile treatment(Lichtenwalner and Sprung, 1970; Lewis, 1967). Because of their widespread use in large numbers of industrial and consumer applications, it appears likely that the geographical consumption and disposal pattern generally follows the same pattern as the U.S. population.

1. Waxes and Polishes

Most furniture, car and glass waxes and polishes contain silicone fluids. They reduce the work required to spread the polish, improve the gloss, and increase the weatherability of the finishes. The silicone content in most polishes varies from 2-10%. Production figures from 20 polish manufacturers estimate that approximately 1,350,000 units of polish and 4,700,000 units of paste were annually produced in the late 1960's(Todd, 1971).

2. Antifoam Applications

Silicone fluids, usually in an emulsified form, have been widely used as antifoaming agents. The extremely small amount of material necessary for activity (0.0001 to 0.02%), makes the use of the defoamer relatively inexpensive. Industries which utilize the silicone antifoams include the chemical, metalworking, paper and printing, plastic and rubber, petrochemical, textile, water and waste water treatment, and food processing industries (Dow Corning, 1972b). It is estimated that quantities of silicone fluids used for antifoaming applications amount to approximately 1 million lbs. annually.

3. Foaming of Polyurethane

Sizable quantities of silicones, in the form of a silicone-polyether (silicone glycols) block - block copolymer fluid, are used to assist in the foaming of polyurethane. The silicone-polyether fluid allows the polyurethane to be foamed in a one step process, the fluid giving control to the pore sizes of the foam (Meals, 1965). The dimethyl silicone portion of the fluid normally consists of 15-30% of the total composition. The copolymer fluids are also used in cosmetic preparations, such as hairsprays, and as paintable mold release agents for plastics (Thimineur, 1972; Meals, 1965). Dow Corning (1973) has estimated the 1973 U.S. market of silicone glycols at 18 million lbs.

4. Release Applications

Silicones represent one of the most important classes of abherents (release agents) (Kovach, 1963). This is a direct application of the low surface tension properties of the silicones. The dimethylsilicone fluid is the most important fluid abherent and it can be applied full strength to the mold being treated, but more frequently the material is in a solution or

emulsion. Silicone abherents are indispensible for high temperature applications such as those found in metal processing and glass molding. Other industries using silicone fluids as release agents include the food, rubber processing, and plastics industries. In some cases, the silicone release agents impart abherent properties to the material being released, which does not allow painting of the released molded part. To overcome this problem, silicone glycols have been used as paintable release agents.

5. Protective Coatings for Textiles, Glass, and Leather

Silicone fluids are frequently used to provide water repellent and smooth textured coatings to textile, glass and leather materials. With glass the methylchlorosilanes were first used to produce silicone films by reacting the methylchlorosilane vapor with water adhering to the glass. Today, the polydimethyl fluids are used as the silicone components. An important part of the treatment process consists of heat treatment (300-400°C) to permanently anchor the fluid to the glass. The silicone fluid allows liquids to drain without leaving any residue behind (important in pharmaceutical preparations) and reduces the breakage rate by affecting the mechanical strength of the glassware.

Silicones used in the textile industry have found ever-increasing acceptance. The fluids have two major advantages over conventional treatments: (1) the finish can be made semipermanent by cross-linking the siloxanes polymer chain, and (2) the finish can be applied in such a dilution that only the fibers are coated thus allowing the passage of water vapor but not liquid water (Ames, 1958). Commonly, the fluid contains a mixture of methylhydrogen- and

dimethylsiloxanes (60:40, Bajaj, 1973) with an organometallic catalyst to assist the cross-linking after the fabric is coated. The silicone treatments resist washing and drycleaning as well as impart a softening and smoothing effect to the textile (Blumenstein, 1968; Noll, 1968).

The silicones are also used in the leather industry to impart water repellency. The silicones are usually applied by immersion of the leather in a dilute silicone solution.

6. Lubricant Applications

The dimethylsilicone fluid's lubricant performance with plastics and rubber is excellent, but because of their poor load bearing capacity (weak intermolecular forces) they are rarely used in high friction applications. However, when combined with fillers to form greases, they are excellent lubricants at extreme heat or cold. Also, if the fluid is chemically modified (e.g. methylphenyl, methylchlorophenyl, or fluoropropyl groups are attached to the silicone), the fluids can be very valuable for extreme temperature friction lubricating problems (Schiefer et al., 1961).

7. Cosmetic Uses

The dimethylsilicone fluids are used in sizable quantities in the cosmetics and toiletries industries. The following properties make them ideal for this application: colorless, odorless, tasteless, resistant to oxidation and do not become rancid, low surface tension (spread easily), incompatible with most organic oils and waxes (spreading aid), water-repellent but allow free passage of water vapor and carbon dioxide, chemically inert (do not react with cosmetic materials), and a very low order of toxicity (Saunders, 1969).

Cosmetic applications include hand, lip, shaving, hair and sun-oil preparations. They are also used in powders, anti-perspirants, and sometimes toothpastes (Thimineur, 1969; Lewis, 1967; Saunders, 1969). The concentration of the fluid in the preparation may vary from 1-5%, although protective creams can contain as much as 20% fluid.

B. Minor Uses

Relatively small amounts of silicone fluids have been used in aerosol starch, domestic oven cleaner and ironing aids (Lewis, 1967). Dow Corning (1972a) recommends their fluids for use in such functions as damping (dash pots, meter indicators, etc.), dielectric cooling and impregnating (power tubes, transformers, capacitors, magnets, electromechanical devices), working media (gyro flotation, shock absorbers, magnetic amplifiers, fluid clutch in rotating equipment, fluid drive in aircraft, diffusion and high vacuum pumps), and heat transfer, as well as the functions discussed in the previous section. The dimethylsilicone fluids have also been cleared by FDA for use as coatings in food-packaging material and as defoaming agents in food. Most of these applications are very specialized and the quantities utilized are relatively small.

C. Discontinued Uses

Lewis (1967) has reported that silicone fluids are no longer used to coat bread baking pans (displaced by fluorocarbon polymer coated pans) or as hydraulic fluids in aircraft applications.

D. Projected or Proposed Uses

Thimineur (1972) has suggested that considerable work is being done by General Electric with dimethylsilicone and silicone glycol fluids as

possible brake fluids for automobiles. Dow Corning (1973) was reported that it is contemplating using fluids as antitranspirants for plants in order to reduce the loss of water in dry terrain. In general, it is anticipated that silicone fluids will be replacing other chemicals in uses that provide human exposure or release to the environment, where the physical properties of the silicones are appropriate and the extra cost is justified.

E. Possible Alternatives to Use

Because silicone fluids are relatively expensive, they are frequently applied only as a last resort. For example, the one shot polyurethane process is designed around the silicone glycols (Bass, 1961). High temperature release applications in the glass and metals processing industries can only be done with silicone abherents (Kovach, 1963). Other antifoaming agents are known, but few work at such low concentrations or are as inert. With some of their bulk applications, such as use as dielectric fluids, hydraulic fluids, and shock absorbers, other chemicals such as epoxy fluids, diphenyl-diphenyloxide mixtures, and other high boiling liquids can be used. However, when it is expected that the application will be exposed to extreme temperatures, the silicone fluids cannot be replaced.

IV. Current Practice

A. Special Handling in Use

Although the organochlorosilane precursors are corrosive, toxic and form hydrogen chloride on contact with water, the siloxane fluids are quite stable at ambient temperatures and relatively physiologically inert. Therefore, no special handling is necessary other than procedures normally followed for inert, low-volatile liquids. No occupational difficulties have been identified (see Section XI, B).

B. Methods of Transport and Storage

The silicone fluids are transported principally in 55 gallon epoxy lined steel drums, although some of the standard dimethylsilicone fluids are sold in carload lots (Lichtenwalner and Sprung, 1970), when they are shipped to big users such as automobile and furniture polish manufacturers. The fluid products are obtainable either as straight oils, or as emulsions or solutions in several types of organic solvents.

C. Disposal Methods

Disposal of silicone fluids are as varied as the many formulations and applications. Unwanted products from production are either incinerated (to CO_2 and SiO_2) or landfilled (Bailey, 1973). Where the fluid is used as a coating, disposal is with the material treated, in refuse dumps or by incineration.

D. Accident Procedures

Because the fluids exhibit a low degree of toxicity and irritability and are not highly flammable, accident procedures are simply oriented at cleanup. Dow Corning (1973) has demonstrated that roadway spills of fluid can be

removed by using finely divided solid absorbents. Roadway spills can also be removed by high pressure streams of water, although this would result in water contamination. When the fluids are spilled on water, they gathered into pools and may be removed by procedures found effective for oil spills.

V. Environmental Contamination

Environmental contamination by silicone fluids deserves special consideration because of the exceptionally inert properties and stability of these chemicals. The long residence time in the environment that may consequently occur as well as the rapid growth in consumption, suggest that although generally inert and non-toxic, the compounds may at some time reach undesirable concentrations. This section will discuss environmental contamination from production, transport and storage, use, and disposal, and then make some projections of possible contamination levels both now and in the future.

A. From Production

Environmental contamination from silicone fluids during the manufacturing operations should not be significant due to the physical properties of the materials. The low volatility and noncorrosive characteristics remove tendencies for the materials to escape or leak from the process steps. Accidental spillages are the exception. Minor losses, however, may accompany other materials that flow from the operation, such as the by-product hydrogen chloride, the wasted impurities from the distillation operations and the salts and wash water from the hydrolysis, neutralizing and washing steps.

The foregoing waste materials and streams are disposed of by clarifications, biological treatment, incineration and neutralization (Bailey, 1973). Any solids and sludges from these operations are disposed in land fills. Loss of silicone fluids to the environment from production operations is, therefore, judged to be relatively low, especially as compared with that which reaches the environment from use and final disposal. However, actual monitoring data is not available.

B. From Transport and Storage

Loss of silicone products during transport and storage is conceivable only as a result of accidental spillage. Because the products are noncorrosive and practically nonvolatile, leakage from containers and storage tanks is unlikely. A possible exception is that residual material left in nonreturnable containers may eventually drain away. The overall loss from transport and storage is considered to be very small.

C. From Use

Of the major silicone fluid uses, the applications for waxes and polishes, antifoams, and cosmetics probably result in the most direct source of environmental contamination. Polishes used on automobiles would eventually wash off and be conveyed to a lake or stream. Similarly, cosmetic preparations would wash off and pass into the sewage system. Antifoams, especially those used in aqueous systems, such as at sewage treatment plants, would directly enter the water systems from the water effluents.

Silicone fluids used in bulk quantities in such applications as lubricants, heat exchange fluids, shock absorbers, and dielectric fluids may also be released directly to the environment either by intentional disposal or through leaks. However, since those applications are a relatively minor part of the fluids market, they are probably not a major source of contamination.

Silicone glycols used in polyurethane foams probably are retained in the foam and eventually deposited in a land fill or incinerated. Release agents eventually wear-off onto the molded product which is again ultimately deposited in a land fill or incinerated. The siloxane coatings of textiles and glass are permanently attached either around the fabric or on the glass wall. However, the treatment baths may be a major source of environmental contamination.

D. From Disposal

Disposal by incineration should result in CO_2 and SiO_2. However, disposal of the fluids in land fills would allow the possibility of leaching into aquatic systems. Such processes are little understood. Permanently bonded protective coatings would probably not migrate from the landfill.

E. General Environmental Contamination

The degree of environmental contamination resulting from commercial use of silicone fluids is unknown. No ambient monitoring data is available. Estimates of environmental release are very crude and amounts used in most applications are unknown. Silicone fluids that might enter the environment are suspected to be persistent (either as the parent fluid or as cyclic species or low molecular weight fragments terminated with silanol groups) and mobile (see Sections VIII and X). Even though the available information is not very exact, we have attempted to make some very approximate estimates of possible concentrations of silicone fluids in the environment.

The Great Lakes drainage basin was taken as a definable area for which calculations could be made. The following assumptions were made:

1. Half of the production of silicone fluids (15×10^6 lbs in 1973) is immediately released to the environment.
2. Rate of production growth of silicone fluids = 10%/year.
3. Residence time of silicone fluids in the environment = infinite.
4. All silicone fluids consumed and released to the environment in the Great Lakes drainage basin are proportional to the U.S. population (~15% of U.S.) and reach the Great Lakes.
5. The Great Lakes have a surface area of 100,000 sq. miles and a volume of about 50×10^{15} ft.^{3}.
6. Effluent flow from the Great Lakes was assumed to be equal to the St. Lawrence flow (~1%/year)

Table X presents the calculations for determining the highest possible concentrations of silicone fluids in the Great Lakes. The concentrations reported in the last two columns assumed that either all the silicones reside evenly dispersed throughout the lake waters or that all the silicones reside in the top one foot of lake sediment. Another possibility not tabulated is that the silicone fluids will reside in a thin layer on the water surface (dimethyl fluids are slightly lighter than water).

The assumptions were purposefully chosen to provide the highest level possible. These estimates can only be considered as an order of magnitude of contamination. The concentrations in Lake Erie could be much higher since it is shallower and is fed by large populated areas. On the other hand, the

following assumptions are probably somewhat high: (a) 10% growth rate in the market, (b) 50% release factor, (c) infinite environmental stability.

Table X. Approximate Highest Concentrations of Silicone Fluids in the Great Lakes

Year	Annual Consumption at 10% Growth Rate		Total Used to Decade	Total Released to Area in the Previous Decade	Balance in Great Lakes	Lost in Lake Effluent 1%/year	Net in Great Lakes System	Average Concentration (ppm)	
	Total for U.S.	Great Lakes Area						Suspended in Lake Water	Deposited in 1 Foot Bottom Silt
1953	0.5	0.1	0.1	<0.1	<0.1	--	<0.1	--	--
1963	12	2	10	5	5+	--	5-	--	--
1973	30	4.5	40	20	25+	2.5	22.5	.0004	0.1
1983	80	12	110	55	80	8	72	.001	0.4
1993	210	32	270	135	215	21.5	193	.003	1
2003	560	85	660	330	545	54.5	490	.01	3
2013	1500	225	1700	850	1395	139.5	1255	.02	7
2023	4000	600	4500	2250	3645	364.5	3280	.06	18

VI. Control Technology

A. Currently Used

Waste water from Union Carbide's silicone plant is neutralized, clarified, and then undergoes secondary biological treatment to remove soluble organics. The sludges are landfilled (Bailey, 1973). Similar water treatment is used by Dow Corning (1973). In general, the liquid and soluble residues from silicone processing are incinerated and the solid wastes are landfilled.

B. Under Development

General Electric Co. has taken out a patent for waste water treatment from silicone manufacturing plants (Lapidot, 1973). The process consists of running the waste water into a flotation and sedimentation basin where the insoluble material is removed. The semipurified water is then adjusted to pH $\geq$ 12 and the alkali water is passed into an ozonizing tank at a rate dependent on the COD level in the water. The purified water is degassed before release.

VII. Monitoring and Analysis

A. Analytical Methods

Although analytical methods for monitoring environmental samples of silicones have not been reported in the surveyed literature, a number of methods have been developed for detecting silicones in the ppm range in food and beverage samples.

Horner, et al. (1960) reported both a specific and non-specific method for detecting trace amounts of silicones in foods and biological material. The nonspecific method consisted of a colorimetric silica analysis of

silicones in foods digested with fuming sulfuric and nitric acids. Jankowiak and LeVier (1971) later modified this procedure in order to eliminate phosphorus interferences. This method is best applicable to samples which contain negligible amounts of residual silica. The high level of silicon occurrences in nature precludes the use of such nonspecific methods for detecting silicones. The specific methods used by Horner, et al. (1960) was a selective extraction of silicone with infrared quantification (7.95 μ band, $(CH_3)_2Si$). The method was utilized in the 2 to 20 ppm range in pineapple juice. Sinclair and Hallam (1971) have used a similar technique to determine polydimethylsiloxane in the 0.2 to 2.00 ppm range in beer and yeast. A low temperature specific extraction of siloxanes from fatty foods with quantification by atomic absorption (nonspecific but more sensitive than IR) or UV spectrometry has been reported by Neal, et al. (1969).

The Dow Corning Corporation (1973) has reported that it uses an extraction procedure to determine low levels of silicones in soil and water. The preferred solvent is methyl isobutyl ketone (MIBK) which can be used directly for the atomic absorption quantification of silicone. Preliminary investigations show this method to be sensitive at the ppb range for water samples.

B. Current Monitoring

No monitoring information on effluent or ambient levels of silicones is available.

VIII. Chemistry

A. Reactions Involved in Use

One of the reasons that silicone fluids are used commercially is a result of their chemical inertness. Thus there are only a few reactions which are involved in their applications. For example, when polymethylhydrogensiloxanes are used in water repellent coatings of textile fibers, they are usually heat cured in order to cause crosslinking between siloxane chains by replacing the Si-H with a Si-O-Si bond. When glass is treated with silicone fluid, the films are fixed by heating, but in this case it is felt that the heat treatment orients the oxygens of the siloxane chain along the surface of the glass (Noll, 1968).

B. Hydrolysis

The SiO bond is about 50% ionic, with silicon the positive member (Meals, 1969). The high heat of formation (108 Kcal/mole) of the Si-O bond makes it very resistant to homolytic cleavage. However, because of its polar nature it is susceptible to heterolytic cleavage - attack by acids or bases (Meals, 1969; Voronkov and Zhagata, 1968; Carmichael et al., 1966; Noll, 1968). However, at neutral pH hardly any hydrolysis takes place. Fox et al. (1950) have suggested that "appreciable" hydrolysis may take place when a large interface exists between water and silicone. Such an interface might occur in an emulsion, aerosol, or a porous polymeric form (Fox et al., 1950). The relative rate of such a process at ambient conditions is unknown, although at elevated temperatures using steam, hydrolysis takes place fairly rapidly (Noll, 1968). The products resulting from hydrolysis would be

silanol-ended (-Si-OH) species, which should be much more water soluble than the parent siloxane.

During the review of the preliminary draft of this report, Dow Corning studied the soil induced hydrolysis and depolymerization of polydimethylsiloxane. Preliminary results of these tests are important enough to have required their being mentioned in the final report. Ingebrightson (1975) observed that a sample of polydimethylsiloxane (100 cSt.) labelled on its methyl groups with C^{14} decayed with a half life of about 10 days when coated on a sample of neutral soil. By this conversion high molecular weight siloxanes were degraded to cyclic species and to low molecular weight fragments terminated with the silanol group. Experimental work is continuing on quantitatively characterizing the nature of the low molecular weight siloxanes.

C. Oxidation

The high heat of formation of the SiO bond results in considerable oxidative stability for siloxane fluids. The polydimethylsiloxane fluids are stable up to 150°C for practically an unlimited time when exposed to air. Above 150°C, the viscosity gradually increases until a gel is formed (in a few hundred hours at 250°C)(Lichtenwalner and Sprung, 1970). The increase in viscosity is caused by the oxidation of the methyl groups to formaldehyde resulting in crosslinking of the siloxane chains by a siloxane bridge. The oxidative stability is increased by replacing the dimethyl

functional groups with methylphenyl or diphenyl groups (Scala and Hickam, 1958). The alkyl substituted fluids are generally less stable than the dimethyl fluids (Meals, 1969). Table XI depicts the gelling time for a variety of silicone fluids. The gelling time is defined as the time in hours for a fluid to gell when it is heated in air at 250°C in a layer 3 mm thick in a glass dish 35 mm in diameter. Ozone does not affect the silicone fluids.

Table XI. Gelling Time of Silicone Fluids
(Noll, 1968, p 460)

Fluid	Gelling Time (hrs)
Methylsilicone	10
Methylphenylsilicone, high MW	
Low phenyl content	400
High phenyl content	1750
Chlorophenylmethyl	
(with addition of iron octoate)	1000

D. Photochemistry

Exposure of silicone fluids to light has a tendency to cause cross-linking of the polymer. For example, Delman et al. (1969) found that exposure of a methylsiloxane resin to a xenon arc lamp (>281 nm) resulted in the formation of Si-CH_2-Si as determined by infrared absorption. When the resin was irradiated with lower wavelengths from a mercury vapor lamp, SiOH and Si-CH_2CH_2-Si linkages were formed.

E. Other

By removing the silicone fluids from exposure to air, the oil remains usable up to temperatures of 200°C. Above that temperature, depolymerization occurs resulting in mixtures of low molecular weight polysiloxanes. The methylphenylsilicone fluids can be used up to 250-300°C in closed systems and in an inert gas up to 400°C (Noll, 1968). In a thermal gravimetric investigation in vacuum, Thomas and Kendrick (1970) postulated that the activation energy of depolymerization is mainly a function of the inductive effect of the substituent group (withdrawing groups increase the activation energy).

At normal temperatures, the siloxanes are stable to metals, wood, paper, plastics, and also to solutions of metal salts, liquid ammonia, and 3% hydrogen peroxide; with concentrated hydrogen peroxide, they give explosive mixtures. The fluids will react, especially at elevated temperatures, with strong mineral acids, particularly hydrofluoric acid, alkalis, and strong oxidizing agents such as concentrated nitric acid or elemental chlorine (Noll, 1968).

IX. BIOLOGY

A. Absorption

Although siloxanes might conceivably be absorbed on inhalation, their physical and chemical properties, as well as their uses and probable environmental fate, suggest that ingestion and skin contact most probably would be the only routes of potential significance. As a rule, long chain polymers are less readily absorbed than their component monomers (Bischoff, 1972). The absorption of most macromolecular compounds often involves either cleavage prior to crossing membrane barriers, or direct phagocytosis. On the basis of available information, the commercially important siloxanes seem to follow this pattern being relatively refractory to either dermal or gastrointestinal absorption (Hine et al, 1969).

In a series of feeding experiments, Frazer (1967a and b, 1968, 1970) did not find significant evidence for the gastrointestinal absorption of a polydimethylsiloxane or an antifoam preparation (96% siloxane, 4% silica) in mice, rats, rabbits, dogs or man. Mice, rats, and dogs were fed 2.5% siloxane x 80 weeks, 1% x 90 days, and 300 mg/kg body weight/day x 120 days, respectively. In these animals, silicate excretion in urine did not rise above control levels, and i.r. spectral analysis failed to reveal siloxanes in various body tissues. In a study on rats, rabbits, and man, failure to absorb the siloxanes was indicated by balance data on the amount ingested and the amount excreted in the feces (see Table XII).

Similar results have been found for a polymethylphenylsiloxane (DC 703 Fluid, viscosity unspecified cSt.). This fluid was fed at 4% of diet along with 16% olive oil to facilitate any potential absorption (Paul and Pover, 1960). Siloxane content was measured as silicon. As indicated in Table XIII, almost all

TABLE XII: Balance data on polydimethylsiloxane ingestion and fecal excretion in rats, rabbits, and man (Frazer, 1967b).

Subject	Siloxane intake in mg.	Siloxane content of faecal samples in mg.		
		Before ingestion of siloxane	After ingestion of siloxane	
Rat 1	270	0	260	
2	270	0	280	
3	270	0	270	
4	270	0	260	
		average	267	(99%)
Rabbit 3	1350	0	1160	
4	1350	0	1060	
		average	1110	(82.5%)
Human subjects				
MS day 8	753	0	725	
" 9	753	0	1356	
" 10	753	0	588	
		average	893	(118.5%)
AC day 8	753	0	1010	
" 9	753	0	Nil	
" 10	753	0	1450	
		average	820	(108.5%)

The relatively low level of siloxane recovery in the rabbits was thought to reflect an error in sampling and fecal consumption (Frazer, 1967b).

Table XIII: Balance data on Polymethylphenylsiloxane (DC 703 Fluid) in rats (Paul and Pover, 1960)

Total Silicon Content In Food Consumed (mg.)	Silicon Content Found in						% Siloxane Recovered
	Gastrointestinal Tract (mg.)	Feces (mg.)	Urine (mg.)	Liver (mg.)	Kidney	Fat Depot	
982.8	-	979.2	-	-	-	-	99.6
1058.4	1.48	1011.0	-	-	-	-	95.7
961.2	2.50	929.9	-	-	-	-	97.0
1071.0	-	1001.0	-	-	-	-	93.4
1063.0	-	975.0	-	-	-	-	91.7
1026.0	1.63	1019.0	-	-	-	-	99.5
944.0	-	898.0	-	-	-	-	95.1

Mean % siloxane fluid recovered = 96.0 $\pm$ 1.0

DC Silicone fluid 703 fed with olive oil and rat cake powder to seven rats for a period of eight days. Tissues and feces were examined for organosilicon compound and urine for soluble silica.

No silicon was found in the lipids of the gastrointestinal tract, faeces, liver, kidney, or fat depot of control animals maintained on a diet of rat cake powder and olive oil.

ingested siloxane was recovered as silicon in the feces or gastrointestinal tract, indicating no siloxane absorption.

Although these high molecular weight siloxanes do not appear to be detectably absorbed across the gastrointestinal membranes, smaller siloxanes of six polymer units or less are absorbed (Bennett, 1973). Specifically, both octamethylcyclotetrasiloxane and 2,6-cis-diphenylhexamethylcyclotetrasiloxane are readily absorbed by monkeys at doses of 1 mg/kg (LeBeau and Gorzinski, 1973) and hexamethyldisiloxane is completely absorbed in monkeys after oral administration of 20-80 mg/kg (Bennett and Statt, 1973).

The siloxanes are less readily absorbed dermally than in oral administration. In humans, polydimethylsiloxane (100 cSt.) and trifluoropropylmethylpolysiloxane (300 cSt.) applied to the back at levels of 50 mg/kg/day, 20 hr/day x 10 days did not result in elevated levels of blood or urinary silicon, indicating no dermal absorption (Hobbs et al, 1972). Under the same conditions of exposure, a cyclic $[(PhMeSiO)_x(Me_2SiO)_y]$ - where $x \geq 1$ and $x + y = 3$ to 8 - was also not absorbed by man (Palazzolo et al, 1972). Even the smallest siloxane, hexamethyldisiloxane, does not irritate rabbit skin on dermal application even though irritation is induced on subcutaneous injection (Rowe et al, 1948).

B. Excretion

As indicated in the previous section, the higher molecular weight siloxanes do not appear to be absorbed and thus, on ingestion, they are eliminated in the feces. This is particularly evident in the data presented from Frazer (1967b) and Paul and Pover (1960). Further, a variety of high molecular weight polydimethylsiloxanes and polymethylphenylsiloxanes have

been shown to exert marked laxative effects on guinea pigs (Rowe et al, 1948, see Table XVII), which is consistent with the premise that these compounds are not absorbed. In the same study, no laxative effect was noted for hexamethyldisiloxane and only a very mild effect for dodecamethylpentasiloxane. This also agrees with absorption data indicating that hexamethyldisiloxane is completely absorbed but that the pentasiloxane approaches the upper limit of gastrointestinal absorption.

The excretory patterns of these lower molecular weight siloxanes have only recently received careful study. Bennett and Statt (1973) indicate that monkeys excrete about 90% of ingested hexamethyldisiloxane after 24 hours. Using ^{14}C-labelled material, 10%-30% was expired, 70%-85% excreted in the urine, and less than 1% in the feces. Octamethylcyclotetrasiloxane and 2,6-cis-diphenylhexamethylcyclotetrasiloxane seem to be excreted somewhat less readily than the disiloxane, with only 89% recovered with 80% of the dose excreted 48 hours after administration. The methylcyclosiloxane had a similar pattern of excretion to the hexamethyldisiloxane: 23.5% in expired air, 55.5% in urine, and 8.4% in feces. The phenyl containing siloxane evidenced a notably different excretion pattern: 3.3% in expired air, 60% in urine, and 28% in the feces (LeBeau and Gorzinski, 1973).

C. Transportation and Distribution

Because the higher molecular weight siloxanes are so little - if at all - absorbed on oral administration, no data on transport or distribution is available for this route with one exception. In a 400 day feeding of polydimethylsiloxane fluid (unspecified viscosity, total dose of 10-29 ml) to rats, no toxic effects were noted but siloxane deposits were reportedly found around the spleen and liver (Polemann and Froitzheim, 1953).

In that a greater percentage of the di- and tetrasiloxanes tested by Bennett and Statt (1973) and LeBeau and Gorzinski (1973) pass through the bile than are excreted by the feces, enterohepatic circulation seems evident.

The distribution of silicones in the body and the transport mechanisms involved in distribution are highly dependent upon the route of administration. Intraperitoneal injection results in high silicone concentrations in the liver, gastrointestinal tract, and fatty tissue (Hine et al, 1969). In contrast to the intraperitoneal route, intracisternal injection results in high concentrations in the brain and vertebral column [see Tables XIV and XV from Hine et al, 1969].

This type of route dependent distribution does not necessarily reflect passive transport mechanisms. When polydimethylsiloxanes (350 and 100 cSt.) are injected intra-articularly - i.e., into the knee joint of the male rabbit - the silicone fluid is gradually removed. However, the rate of loss does not vary with the degree of joint immobilization, thus suggesting an active distribution mechanism (Donahue et al, 1971). Artifically induced blood transport has been examined by I.V. injections but to what extent the circulatory system is used naturally is not clear (Reed and Kittle, 1959). The commonly noticed distribution of silicones in the kidney and liver might be explained in terms of filtration of silicones from the blood but further experimentation is necessary (Nosanchuck, 1968; Cutting, 1952). Because of the general impermeability of membrane systems to siloxanes, phagocytosis by wandering cells may also be a prime method of transport (Hine et al, 1969; Bennett, 1973).

TABLE XIV: Distribution of ^{14}C-labelled silicone in rat tissues 25 days after intraperitoneal injection of 15 µCi per rat (Hine et al, 1969)

Tissue	rat number 1	2	3	Average percent activity/organ[a]
Fat	-	59.00	43.00	51.00
Heart	0.00	0.00	0.00	0.00
Kidney	-	0.74	0.51	0.63
Liver	-	16.1	13.5	14.80
Lung	0.08	0.05	0.08	0.07
Muscle	1.50	0.82	0.79	0.10
Skin	0.08	0.10	0.097	0.09
Brain	0.03	-	0.05	0.04
Spleen	2.80	0.17	0.30	1.56
Testes	-	1.70	0.12	0.98
Whole blood	0.00	0.00	0.00	0.00
Gastrointestinal	-	16.80	37.70	27.25

[a]Percent activity based on total counts received.

TABLE XV: Distribution of ^{14}C-labelled silicone in rat tissues 45 days after intracisternal injection of 6 µCi per rat (Hine et al, 1969)

Tissue	rat number 1	2	3	4	Average percent activity/organ[a]
Fat	5.0	6.1	10.0	10.3	7.9
Brain	38.9	43.4	40.0	42.0	41.1
Vertebral column	33.9	32.0	27.9	32.0	31.4
Spinal cord	8.5	12.6	6.5	12.0	9.9
Spleen	0.09	0.58	0.0	0.16	0.21
Lungs	0.36	0.04	0.06	0.20	0.16
Liver	1.78	2.96	0.0	0.0	1.19
Gastrointestinal tract	0.0	0.0	0.0	0.0	0.0
Whole blood	0.0	0.0	0.0	0.0	0.0

[a]Average of 4 animals.

D. Metabolic Effects

The siloxanes have not been extensively studied for metabolic effects *per se*. Metabolic effects may be inferred based on toxicity data but they have not been demonstrated *in vivo*. Franklin (1972) has shown that a pure polydimethylsiloxane (unspecified viscosity) as well as various antifoams produce a type I substrate binding spectrum in rat hepatic microsomal suspensions. The pure siloxane, however, produced this effect only after sonication was used to disperse the compound in the suspension. It should be emphasized that this study was undertaken primarily because siloxane antifoams are used in microsomal studies and the relevance of this effect to *in vivo* conditions has not been demonstrated.

E. Metabolism

Dow Corning Corporation recently completed a study for the World Health Organization on the metabolism of polydimethylsiloxanes in mice, rats, and primates including man. The results have been submitted (Bennett and Statt, 1974) but are not included in this review.

X. Environmental Transport and Fate

A. Persistence

The stability of silicones under environmental conditions has not received a great deal of study. The available information is discussed in the following two sections.

B. Biological Degradation

A number of studies have shown that microorganisms may grow on the surface of silicone rubbers and resins but will not degrade them (Greathouse et al., 1951; Glazar, 1954; Hueck, 1960; Ross, 1963; Caldron and Staffeldt, 1965; Muraoka, 1966; Zharikova et al., 1971; Inoue, 1973). However, the silicone fluids have not been as intensely studied. Olson and coworkers (1952) reported that coating cotton with silicone fluids made the textile more resistant to biodeterioration. In a study of the possible biodegradation of cosmetic ingredients, Yanagi and Ouishi (1971), using pure cultures of 23 strains of bacteria, 25 strains of yeasts, and 17 strains of fungi, found that the dimethyl and methylphenyl silicones tested could not be utilized by the organisms. In a comprehensive biodeterioration appraisal of silicones, Sharp and Eggins (1970) concluded that dimethyl silicones were resistant to deterioration by common fungi. They find no difference between the pure cultures of fungi isolated from a soil perfusion apparatus used with or without silicone fluids (0.65, 2.0, and 3.0 cSt.).

Dow Corning has evaluated the effect of polydimethylsiloxane fluids of varying viscosities on the growth of bacterial species. The fluids were non-toxic, but the organisms could not grow without exogenous nutrients.

Examination of the fluids (20 cSt. and 100 cSt.) showed no alteration in the molecular distribution of the fluid components following the growth of E. coli and S. aureus (Bennett, 1973).

Both Union Carbide and Dow Corning have run biodegradability tests on silicone fluids. Union Carbide (Waggy, 1971) determined the stability a silicone fluid (50 cSt.) (330 ppm) and two silicone glycol fluids (660 ppm and 1000 ppm) with a Warburg respirometer system and dilution bottle BOD procedure (silicone glycol only). These compounds were found to be completely nonbiodegradable.

Dow Corning (Hobbs, 1973) ran a 70 day aerobic biodegradability test on ^{14}C-labelled dimethylpolysiloxane exposed to sewage microorganisms. No biodegradability was noted under the experimental conditions.

C. Chemical Stability in the Environment

Ingebrightson (1975) has recently observed a half life of 10 days for a C^{14} methyl labelled polydimethylsiloxane (100 cSt.) coated on neutral soil. The high molecular weight siloxanes were converted to cyclic species and to low molecular weight fragments terminated with silanol group ($-Si(CH_3)_2-OH$. See section VIII, B for further information on acid/base catalyzed hydrolysis.

D. Environmental Transport

Little information is known about the transport of silicones through the environment mainly because of the lack of monitoring data. Dow Corning (1973) has conducted some preliminary studies on leaching properties of the polydimethylsiloxanes in soil. With damp soil they have concluded that silicones are fairly mobile. The vapor pressure of silicone fluids (10^{-5}-10^{-6} mmHg)

is similar to PCB's (10^{-4}-10^{-6} mmHg) and DDT's (10^{-5}-10^{-7} mmHg), and, therefore, atmospheric transport may be an important environmental route.

If the soil induced depolymerization noted by Ingebrightson (1975) occurs at appreciable rates [illegible] re, the resulting products (cyclic products and lower molecular weight s[illegible]s) should be significantly more mobile in the environment. The cyclic materials will be much more volatile (boiling point of trimer and tetramer are 134°C and 175°C, respectively). The silanols should be considerably more water soluble, suggesting water transport and leaching from landfills as important transport processes.

E. Bioaccumulation

Although bioaccumulation studies of silicones in low trophic levels of the food chain have not been reported, some study with fish has been undertaken by Dow Corning (Hobbs, 1973). Bluegill sunfish were exposed to ^{14}C-labelled polydimethylsiloxane for 30 days at 1 and 10 ppm. No evidence of accumulation was observed and the tissue storage in these fish was minimal. Studies on bioaccumulation of products of the soil induced depolymerization have not been reported.

XI. TOXICITY - HUMAN EXPOSURE

Pure preparations of commercially important liquid siloxanes are generally considered to have very low levels of biological activity (see Section XII., Toxicity to Birds and Mammals). Because of this and their unique physical and chemical properties, these siloxanes are widely used as additives in a variety of commercial products to which humans may be exposed by ingestion (food addivites), dermal absorption (e.g. shampoos and hand lotions), or inhalation (e.g. aerosol products including antiperspirants, hair sprays, and insect repellents). In addition, liquid siloxanes have found broad areas of application in the biomedical sciences including use in soft tissue augmentation or reconstruction, antifoaming agents during extracorporeal circulation, and as lubricants in a variety of procedures. It is important to emphasize that almost all of these uses involve or have involved liquid siloxanes with additives rather than the pure polymer. In normal consumer use - food, cosmetic, aerosols - there is no concrete evidence and barely a suggestion that the commonly used liquid siloxanes are in any way detrimental to humans. Although the various medical uses have stimulated some controversy, evidence for adverse tissue reactions caused by the pure polymer is at best equivocal. However, low levels of biological activity and toxicity are not to be equated with biological inertness or lack of toxicity. Thus, discussing human exposure to the liquid siloxanes in an attempt to assess their environmental safety, emphasis will be placed not only on their apparent harmlessness but also on studies defining some degree of biological activity or indicating a need for such definition in a specific area.

A. Controlled Studies

For the most part, toxicity studies on non-human mammals and information in other areas of human exposure have not indicated the need for extensive controlled testing in humans. A pilot study has been recently completed on the absorption, metabolism and elimination of polydimethylsiloxane in humans (Bennett and Statt, 1974). In that silicones are used widely in the cosmetics industry (Thimineur, 1969), polydimethylsiloxanes (20, 50, and 100 cSt.) have been tested and found not to be fatiguing, irritating, or sensitizing to human skin on repeated insult patch tests (Barry, 1973). Four human volunteers were fed a 7530 mg. mixture of 6% silicon dioxide and 94% polydimethylsiloxane (1000 cSt.) for ten days. Neither adverse affects nor intestinal absorption were noted (Frazer, 1967b).

B. Occupational Studies

Certain compounds used in the manufacture of various siloxanes are highly toxic: these compounds include silicon tetrachloride, the chlorosilanes, and tetraethyl orthosilicate (Rowe et al., 1948; Taylor, 1950). However, the commonly used siloxanes themselves are not considered to be hazardous under conditions of occupational exposure (Baily, 1973; Taylor, 1950). Frequently, very slight transient conjunctivitis is noted among users from either vapor or direct exposure to these siloxanes. This probably results from the inability of the lacrimal gland to lubricate the eye due to the hydrophobic properties of the siloxanes (Hobbs, 1973). The type of irritation has been described as similar to wind burn (Rowe et al., 1948). However, claims of conjunctivitis resulting from vapor exposure seem questionable in that the vapor pressure of most commercial fluid siloxanes would result in concentrations not exceeding 1 ppb in confined atmospheres. In such cases, either volatile

additives in the commercial preparation or incidental direct contact may be factors. Similarly, an individual spraying a water-proofing silicone-petroleum-solvent material over a four hour period developed severe pulmonary complications. Subsequent investigation revealed that the petroleum rather than the siloxane was the damaging agent (Horn et al., 1957).

C. Epidemiology

The liquid siloxanes have resulted in no documented wide-spread syndrome of adverse affects and thus have not warranted epidemiologic investigations in the strictest sense of the term. Studies have not shown a correlation between mammaplasty and breast cancer (Bowers and Radlauer, 1969; Hoopes et al., 1967).

The only other study relating to epidemiology was conducted by Talbot and Meade (1971). During the course of a routine anticoagulant clinic, these investigators noted that several patients under treatment with warfarin or phenindione had elevated thrombotest percentages indicating either insufficient dosage or some interfering agent. During questioning, all of these patients indicated that they consumed potato chips cooked in an oil containing additives "allied" to the polydimethylsiloxanes. When this product was eliminated from the diet for seven days, thrombotest percentages returned to normal without alteration of anticoagulant dosage (Talbot and Meade, 1971). These investigators have since warned their patients not to consume this product but have conducted no experimental tests to validate the highly circumstantial association between the polydimethylsiloxanes and decreased activity of anticoagulant drugs (Meade, 1974). No futher investigations into this potential effect have been encountered.

The apparent lack of interest in this effect is not difficult to fathom. As mentioned previously, the polydimethylsiloxanes are used in a variety of foods. They have been approved by the F.D.A. in dietary doses of up to 10 ppm in most foods and up to 16 ppm in gelatin desserts (F.D.A., 1972). Further, these compounds are used as antiflatulents at a suggested dose of 160 mg/day for man (Hobbs, 1973) and are present in a number of antiacid preparations. Freeman and coworkers (1973) have reported that foods fried in siloxane containing oils have a siloxane residue of approximately 1 ppm. These results have been confirmed in further research using tritium labelled siloxane (Freeman, 1974). Thus, if the polydimethylsiloxanes did result in appreciable altered metabolism of the anticoagulant or anticoagulant malabsorption, it seems reasonable to expect that this condition would have been noted by many clinicians involved in anticoagulant therapy. Nonetheless, it is regrettable that this admittedly tenuous connection has not been pursued with at least some preliminary testing. These compounds are widely consumed and prescribed largely on the basis of their reputed lack of adverse effects: the onus of maintaining this reputation would seem to fall on those who would recommend their use.

D. Medical Applications

The study of the medical uses of compounds such as the polydimethylsiloxanes might seem remote to their potential environmental effects. However, such uses have stimulated by far the most detailed evaluation of these compounds in a biological system. Consequently, indications of biological activity in these applications might serve to designate specific areas in which environmentally oriented questions may arise. Even accepting this line of reasoning, however, only three broad applications need be considered: retinal detachment therapy, antifoams and lubricants, and soft tissue augmentation.

1. Retinal Detachment Therapy

Various polydimethylsiloxane fluids (350-4500 cSt.) have been injected into the vitreous as therapy for complicated forms of retinal detachments, such as massive pre-retinal retraction and/or giant retinal breaks. In some instances, this treatment is beneficial and the siloxanes seem well-tolerated. After this treatment, Labelle and Okun (1972) noted improvement in 13 patients suffering from retinal detachments and massive pre-retinal retraction over a four to ten year period. In a group of 200 patients, intravetreous injection of polydimethylsiloxanes (400, 1000, and 2000 cSt.) resulted in immediate retachment in 79 patients and improvements in visual acuity for 64 patients and a broadening in the visual field in 61 patients. The retachments were maintained by 56 patients and improvements were maintained by 44 patients in each category for periods of up to three years (Muratova, 1971). However, other investigators and clinicians have noted either unsatisfactory results, late complications, and/or adverse reactions apparently to the siloxane. In 100 cases of retinal detachments treated with siloxane injections, Cockerham and coworkers (1970) noted success in only eleven cases. Noting the potential complications such as corneal damage due to siloxane mobility in the anterior chamber, cataract formation, and corneal opacification, they recommend the procedure only as a last alternative. Formation of siloxane bubbles in the anterior chamber of a patient two years after treatment, followed by corneal degeneration has also been noted. In this patient, siloxanes were frequently associated with pigment dissemination and found in the iris, stroma, retina, and corneal scar. While not indicating any definite adverse

tissue response, this study does attest to a considerable degree of mobility (Blodi, 1971). Retinal destruction has been attributed directly to the injection of siloxane in a female patient after six years (Hoppenbrouwers and Lanberg, 1971). These rather disparate clinical results have stimulated detailed studies on non-human mammals in terms of both the efficacy of the procedure and the possibility of adverse tissue responses to the siloxanes (see Section XII, Toxicity to Mammals).

2. Antifoams and Lubricants:

These two uses are somewhat interrelated in that both may involve intravenous injection. However, many lubricant uses, such as lubrication of urethra and endoscopic instruments during insertion, do not involve intravenous exposures, and in that no adverse effects attributable to the siloxane have been reported, such applications need not be detailed (Lapides et al., 1968). Medical grade polydimethylsiloxane (200 cSt.) has also been used as lubricants in disposable syringes. Miller and coworkers (1969) have noted that in such syringes having visible accumulations of siloxanes on the tips of the plungers this material may be released during injection by mechanical flushing action. The quantities released ranged from 0.8 to 4.5 ug/injection in 10 ml. plastic syringes. No reports of adverse effects from this use have been encountered. Similarly, pure liquid siloxanes have also been used as lubricants in artificial joints without marked adverse effects (Helal, 1968).

Unlike their use as lubricants, the siloxanes used as antifoaming agents are not pure preparations but rather mixtures of polydimethylsiloxanes and various other agents. The most commonly studied siloxane antifoaming

agent is DC Antifoam A, a mixture of polydimethylsiloxane with 4-4.5% silica. This type of mixture is sometimes combined in oil and water emulsions with compounds such as glyceryl monostearate and propylene glycol monolaurate (Kimura et al., 1964). Polydimethylsiloxane/silica preparations have been used as antifoaming agents in pump-oxygenators during extracorporeal circulation and have been associated with the formation of emboli. A study conducted by Thomassen and coworkers (1961) noted silica deposits in the brains and livers of all eleven patients receiving this treatment and similar deposits in hearts, lungs, spleen and kidney in several of these patients. Polydimethylsiloxane deposits were not noted. Although Helal (1968) noted that embolisms may result from intravascular injection of pure siloxanes, such adverse effects have not been demonstrated in man from normal medical uses.

3. Soft Tissue Augmentation:

The fluid polydimethylsiloxanes have been used widely for the augmentation of soft tissue. These applications have been reviewed and summarized periodically (Ashley et al., 1967; Ashley et al., 1971; Braley, 1973; Lejour and Mattin, 1971). Of these procedures, mammaplasty - enlargement of the breast by insertion of a foreign material - has received the most attention because of the many adverse effects reported from this procedure. Mammaplasty with siloxanes can be accomplished in two basic ways, either by direct injection of the polydimethylsiloxane fluid into the breast or by surgically implanting a mammary prosthesis containing various siloxane products. In that this latter method does not involve direct fluid siloxane-tissue contact, it need not be considered (see Braley, 1973; Johnson, 1969; Vrebos, 1972).

Polydimethylsiloxanes may be injected either in pure form or with additives. When injecting pure siloxanes the primary complication is siloxane mobility from the injection site. Injection of pure siloxanes into the breast has resulted in the gravitational migration of the siloxanes to the inguinal regions and the abdominal wall (Delage et al., 1973). Similar but less extreme mobility of injected siloxanes has been noted by Boo-Chai (1969) as one of the major complications in dealing with pure preparations of polydimethylsiloxanes. Siloxane mobility may be attributed at least in part to its low degree of tissue reactivity. This is unlike the behavior of many organic preparations such as vegetable fatty acids which will cause relatively rapid tissue response with cyst formation and subsequent immobility. Consequently, in order to reduce mobility, reactive ingredients such as vegetable oil are sometimes added to injectable siloxane preparations (Braley, 1970). A common preparation of this type is the "Sakurai formula" consisting of about 99% polydimethylsiloxane and 1% animal or vegetable fatty acids (Kagan, 1963). It seems that from such adulterated preparations, the major cases of "adverse tissue responses to siloxanes" have arisen. Winer and coworkers (1964), Chaplin (1969), Nosanchuk (1968), and Symmers (1968) have all reported severe adverse tissue responses to "silicone" injection in the breast. In only one of the cases reported (Symmers, 1968, Case 2), however, is there an even reasonable indication that the original injection contained only pure siloxanes (reportedly 400 ml. DC 360 Medical Grade Fluid). In this individual periodic reinjections had been necessary to maintain desired contour apparently indicating marked migration. Histologic examination of mammary nodules noted sclerosing granuloma and fat necrosis. If based on such studies,

the use of such phrases as "silicone granuloma" or "silicone mastitis" may well be inappropriate, with a more plausable cause being organic additives (Nosanchuk, 1968; Braley, 1970; Helal, 1968). However, while many of the most severe complications of "silicone" injections may not be caused by the polydimethylsiloxanes, there are some indications that these pure compounds are not entirely inert. Boo-Chai (1969) cites inflammation with severe pain as the most troublesome complication of pure siloxane injection. Sometimes, this condition is only temporarily relieved by broad spectrum antibiotics and anti-inflammatory agents and the siloxane must be removed. Delage and coworkers (1973) have strongly implicated unadulterated polydimethylsiloxanes in a foreign-body granulomatous reaction. In a woman receiving siloxane injections two and a half years previously, multicystic masses were noted surrounded by foreign-body giant cells and containing pure polydimethylsiloxane identified by infrared spectrophotometry. Although the initial injection reportedly consisted of pure polydimethylsiloxanes, the potential influence of unrecognized impurities cannot be ruled out.

Thus, the role of siloxanes in causing adverse tissue responses in man is still rather questionable. Even though such operations are prohibited in the United States, siloxane involvement in serious complications has not been conclusively demonstrated (Bischoff, 1972), although it often seems to be assumed by association (e.g. Malbec, 1967). Siloxanes have been injected into other sites using smaller quantities with highly therapeutic results such as in cases of facial hemiatrophy (Ashley et al., 1971). Conversely, injection into areas not suited to this type of soft tissue augmentation may be detrimental (Datta and Kern, 1973).

XII. TOXICITY TO BIRDS AND MAMMALS (Other than man)

Ever since the initial investigations of Rowe and coworkers (1948), the commercially important silicon containing polymers have generally been considered to have a low order of both toxicity and biological activity. As might be inferred from the discussion of siloxane absorption, the low order of oral toxicity may in part be attributed to their lack of absorption. However, siloxanes have also been tested by various routes of injection and, while not inert, do not seem to act as specific toxicants but rather exert their effects as a function of their physical-chemical properties or as non-specific foreign body irritants. Bischoff (1972) has recently reviewed the general question of the biological activity of synthetic organic polymers.

In contrast to the high molecular weight polymers, silicon containing non-polymeric molecules can have a very high degree of biological activity. Some general classes are presented in Table XVI.

Table XVI: Biologically active organosilicon compounds (Voronkov, 1973)

Type of effect	Class of organosilicon compounds*	Type of effect	Class of organosilicon compounds
Impairment of co-ordination of movement	$R_3SiZNR'R^*$ $R_{4-n}Si(OCH_2CH_2NR_2')_n$ $(R_3SiOCH_2CH_2)_nNH_{3-n}$ $RSi(OCHR'CH_2)_3N$	Insecticidal activity	$R_{4-n}Si(NCS)_n$ $R_3Si(CH_2)_nNR'R^*$ $R_3Si(CH_2)_nNR'R^*$ $R_3SiC\equiv C-CH_2$
Reduction of blood pressure	$[R_3SiCH_2N(CH_3)_2CH_2CH_2X]^+Y^-$ $R_3SiC\equiv C-C(OH)R'R^*$	Fungistatic activity	$R_{4-n}Si(SCN)_n$
Stimulation of breathing	$RSi(OCHR'CH_2)_3N$ $[R_3SiCH_2N(CH_3)_2CH_2CH_2X]^+Y^-$ $[R_3SiOCH_2CH_2N(CH_3)]^+X^-$ $R_3SiCH_2CH(COCH_3)CH_2NRR'$ $R_3SiC\equiv C(OH)R'R^*$	Insect repellent activity Antibacterial activity	$R_3Si(CH_2)_nCH_m(SCN)_{3-m}$ $RR'NCH_2(CH_3)Si(OR)_2$ $R_3SiZNR'R^*$
Soporific activity	R_3SiOH, R_3SiNCO	Zoocidal activity	$RSi(OCHR'CH_2)_3N$

* R,R',R* = Hydrocarbon or alkoxyl radical; Z = saturated or unsaturated, substituted or unsubstituted three-carbon chain; X, Y = halogen, OH, OCOR'.

As an example, the silatrane, 1-(p-chlorophenyl)2,8,9-trioxa-5-aza-1-siabicyclo[3.3.3] undecane, has been developed as a rodenticide (Beiter et al., 1970). The biological activity of these non-polymeric silicon compounds has been well reviewed by Fessenden and Fessenden (1967) and Garson and Kirchner (1971), the latter presenting acute lethality data on over a hundred such compounds. While indicating that silicon substitution does not in itself insure low toxicity or biological inactivity, it must be emphasized that the siloxane polymers would most probably not degrade to such compounds.

Of the commercially important siloxane classes, only the two most common - polydimethylsiloxane and polymethylphenylsiloxane - have been extensively tested for toxicity. Of these, the dimethyl is the most widely used and has generated the most detailed investigations. In addition, various formulations of these compounds, particularly the antifoaming agents, have been screened for toxicity. As in the human studies, care must be taken in such studies to differentiate the toxic effects of the polymer from those of the additives. Further paralleling the human investigations, ingestion, as the most common route of entry, has received the greatest emphasis. Alternate routes such as inhalation, dermal absorption, and various routes of injection have also been tested reflecting the commercial and medical uses of these compounds.

A. Ingestion

1. Acute Oral Toxicity (1-14 Days)

The siloxane polymers have an extremely low order of acute oral toxicity. This was first demonstrated by Rowe and coworkers (1948) in single dose intubations of a series of dimethyl and methylphenyl siloxanes to

guinea pigs. The results of these experiments are given in Table XVII.

Table XVII: Acute oral toxicity of single doses of various siloxanes to guinea pigs. (Rowe et al., 1948)

Siloxane	Viscosity in cSt. at 25°C.	Dose* ml./kg.	Mortality Ratio	Observations on the Laxative Effects at Various Periods of Time After Administration — Hours			
				2½	8	24	48
Hexamethyldisiloxane (DC 200 Fluid)	0.65	3.0	0/7				
		10.0	0/7	-	-	-	-
		30.0	0/7	-	-	-	-
		50.0	1/10				
Dodecamethylpentasiloxane (DC 200 Fluid)	2.0	10.0	0/3	-	+	-	
		30.0	0/6	-	++	-	-
		50.0	3/3				
Polydimethylsiloxane (DC 200 Fluid)	50	10.0	0/2	+++	+++	+++	+
		30.0	0/6	+++	+++	+++	+++
		50.0	0/3				
Polymethylphenylsiloxane (DC 550 Fluid)	75	3.0	0/3				
		10.0	0/3	+	+	+	
		30.0	0/6		++	+++	+++
Polymethylphenylsiloxane (DC 702 Fluid)	35	3.0	0/3				
		10.0	0/3	+	++	+++	
		30.0	0/6		++	+++	++
Polydimethylsiloxane (DC 200 Fluid)	350	5.0	0/2	-	-	+	
		10.0	0/5	-	+	+	-
		30.0	0/6	-	+	+	-
		50.0	0/3	-	-	++	++
Polydimethylsiloxane (DC 200 Fluid)	12,500	Could not be fed satisfactorily					
Mineral Oil U.S.P.		10.0	0/2	++	++	+++	+
		30.0	0/3	+++	+++	+++	+

* Dose administered as 5 ml/30 minutes in doses greater than 5 ml.

Even at extremely high doses, only the lower molecular weight siloxanes produced any marked toxic effects. Between two and a half and forty-eight hours, the higher molecular weight siloxanes produced only mild laxative effects. In that the less viscous compounds produced this effect more quickly and to a greater extent would seem to indicate that the laxative action reflects the lubricant effect of these compounds in the intestinal tract. Hexamethyldisiloxane did not produce any laxative effect but did result in one death and mild intoxication and central nervous system depression hours (unspecified) after intubation of 50 ml/kg. Dodecamethylpentasiloxane causes more marked lethality at 50 ml/kg but no apparent central nervous system depression and only a mild laxative effect (Rowe et al., 1948). This is consistent with Bennett's (1973) explanation of siloxane absorption - only compounds of six polymer units or less are absorbed to any marked extent-and with the low and possibly zero level of DC 703 absorption in rats noted by Paul and Pover (1960). The mechanism of CNS depression shown by hexamethyldisiloxane cannot be inferred from the data presented by Rowe and coworkers (1948). Similar intubation of rats and rabbits of doses up to 54.0 ml/kg. polydimethylsiloxane (DC. 200, 100 cSt) and 36.0 ml/kg polymethylphenylsiloxane (DC 701, 9.2 cSt. at 25°C) resulted only in transitory weight loss without pathological changes being noted in tissues (Treon et al., 1954).

Somewhat longer term acute feeding studies have been conducted with polydimethylsiloxane administered in the diet rather than by intubation. Rats and rabbits have been administered DC Antifoam A dispersed in olive oil (Frazer, 1967b). The doses of polydimethylsiloxane (1000 cSt.) contained in this mixture were 270 mg. for rats and 1350 mg. for rabbits. No signs of

toxicity were noted. Til and Spanjers (1971a and b; 1972) and Til and coworkers (1971a and b) have also tested the acute oral toxicity to rats of both silicic acid and non-ionic emulsions of siloxanes and found LD_{50}s of single oral administrations above 30 ml/kg with no signs of toxicity 14 days after administration on autopsy.

Although mammals have been most widely tested to determine siloxane toxicity, 5 day feeding studies of a polydimethylsiloxane (100 cSt.) in mallard ducklings (Fletcher, 1973a) and bobwhite quail (Fletcher, 1973b) have been carried out. In both experiments, the birds were fed ad libitum a commercial bird diet containing polydimethylsiloxane levels of 312.5, 625.0, 1250.0, 2500.0, and 5000 ppm. Both negative (no siloxane) and positive (dieldrin) control groups were used. The animals were fed the siloxane containing mixture for five days and allowed a three day recovery period before sacrifice and autopsy. None of the siloxane fed quail died and no signs of toxicity, adverse gross pathology, abnormal weight gain or food consumption were noted (Fletcher, 1973b). Similarly, in the experiment using ducklings, no signs of toxicity, adverse gross pathology, abnormal weight gain or food consumption were seen although one of the ducklings fed the 625.0 ppm siloxane diet died on the second day of feeding (Fletcher, 1973a). In the absence of any clear indications of toxicity or lethality at higher dose levels, this one death is probably insignificant.

2. Subacute Oral Toxicity (15-90 Days)

In preliminary investigations on the subacute oral toxicity of the siloxanes, Rowe and coworkers (1948) intubated rats with polydimethylsiloxane (35 cSt.) once a day for 28 days at doses of 1.0 to 20.0 g/kg/day. No changes from controls were seen in growth rate, hematology, organ weights, or histopathologic examination of the heart, spleen, liver, kidney, adrenals, pancreas, bone marrow, stomach, and intestine.

Ninety-day feeding studies have been conducted by three groups of investigators. MacDonald and coworkers (1960) fed polydimethylsiloxanes (50, 350, 1000, 10000, and 60000 cSt.) at levels of 10,000 ppm in chow to rats for 90 days. On an average, each rat consumed 175-192 mg of the siloxane per day. No adverse effects were noted in food consumption, weight gain, tissue weight, or on pathological examination. DC Antifoam A (viscosity not specified) has also been fed to rats at dietary levels of 1000, 2000, and 10000 ppm for 90 days (Rowe et al., 1948). No adverse effects were noted on blood urea nitrogen, organ weights, or on pathological examination. Frazer (1967a) has also fed rats DC Antifoam A (1000 cSt.) at dietary levels of 1000 and 10000 ppm for 90 days. As in the previous studies, no adverse effects were noted in blood chemistry, weight gain, tissue weights, or tissue pathology.

3. Chronic Oral Toxicity (91 Days and Longer)

Of the commercial siloxanes, only the antifoams have been tested for oral toxicity over prolonged periods. An antifoaming agent (1000 cSt.) containing 94% polydimethylsiloxane and 6% silicon dioxide were fed to beagle dogs at 300 mg/kg/day for 120 days (Frazer, 1968). The total siloxane consumed was between 300 and 500 g. No adverse effects attributable to the siloxane were noted on weight gain, blood formation, serum urea, liver function, serum electrolytes or tissue pathology. Frazer (1970) also fed the same compound to mice over an 80 week period at levels of 2500 and 25000 ppm. No toxic effects due to the dietary siloxanes were noted based on survival rates and pathology. DC Antifoam A has been tested in long term feeding studies on both rats (Rowe et al., 1950) and dogs (Child et al., 1951). Rats fed 3g/kg feed for two years developed no signs of toxicity based on weight gain, organ weights, blood count, urea nitrogen, liver lipids, or pathology (Rowe et al., 1950). The dogs were fed 0.3, 1.0, and 3.0 g/kg feed for 6 months. Weight gain was normal in all groups but in all siloxane fed animals bile deposits were found in the Kupffer and hepatic cells, the quantities of such deposits being directly related to dietary siloxane levels. In the group receiving the highest dose, such deposits were also found in the interlobular bile ducts. The investigators were not able to explain the significance - if any - of these deposits (Child et al., 1951).

4. Siloxanes and Cholesterol Metabolism

The previous studies on the oral toxicity of the siloxanes might be characterized as "standard" toxicity tests - i.e., studies monitoring biological parameters such as weight gain, relative tissue weights, and

lethality, which are frequently altered by common toxic agents. Such tests might fail to indicate certain very specific types of biological effects of agents having a narrow range of biological activity. There is some indication that polydimethylsiloxanes and/or polymethylphenylsiloxanes may have this type of biological specificity in exerting an influence on cholesterol absorption and/or metabolism.

Cutting (1952) fed rats a diet containing 20,000 ppm DC Antifoam A over a four month period and noted no toxic effects. In the same experiment, a polydimethylsiloxane (DC 200) at 10,000 ppm in feed and DC Antifoam A at 250 ppm in feed were given to rabbits along with 8000 ppm cholesterol over a three to four month period. In the rabbits fed DC 200 with cholesterol, microscopic examination of the kidneys revealed renal tubular damage. A clear material was seen which did not stain with hemotoxylin and iosin or Sudan IV (fat positive stain). Brown pigment and a foamy cytoplasm were found in some tubular cells. None of these changes were seen in the rabbits fed cholesterol without DC 200. The rabbits fed DC Antifoam A with cholesterol evidenced wide spread cellular infiltrations, especially in the kidney and liver.

The histologic damage in rabbits attributed to the siloxanes by Cutting (1952) is disputed by Carson and coworkers (1966). These investigators used two sets of controls, unaltered basal chow and 8000 ppm cholesterol in an eight month feeding to rabbits of both 10 g/kg DC 360 (350 cSt.) and 10 g/kg DC Antifoam A with and without a 8000 ppm cholesterol supplement. The histopathological findings in rabbits are given in Table XVIII.

Table XVIII: Histopathology in rabbits after 8 months of specified diet (Carson et al., 1966).

Organ and Findings	Control	Cholesterol	DC 360 350 cSt	DC 360 350 cSt +Chol.	DC 360 50 cSt	Antifoam A	Antifoam A + Cholesterol
Liver							
Fibrosis, periportal		2		3			
Cirrhosis	1	1					2
Biliary obstruction	1						
Fat in vessels	1						1
Vacuolated hepatic cells		4					
Hepatic cells with foam cytoplasm	1			5			3
Foamy deposits				1			
Fibrosis		2					
Liver							
Hemosiderosis	3		1	3		1	
Foam cells		3		2			
Foam cells in red pulp				1			4
Foamy deposits				1			
Gastrointestinal tract							
Foam cells in mucosa and muscle	1			1			1
Kidneys							
Foam cells		1					2
Foam cells in pelvis	1			1			
Foamy deposits				1			
Focal chronic inflammation	2				3		
Dilated tubules		1					
Sclerosis of vessels	1						
Protein casts		1					
Foci of scarring	2						
Interstitial foamy deposits in medulla							2
Adrenals							
Foam cells		3					1
Foam cells in cortex		1					
Foam cells in medulla	2	1					
Foamy deposits in parenchymatous cells			1	6			
Lymph nodes							
Foamy deposits				5			
Heart							
Foam cells in coronary vessels	1			4			
Fatty material in vessels		2					
Myocarditis	7	1					2
Endocardial thrombus with underlying inflammation in myocardium			1				
Fibrosis, interstitial							2
Aorta							
Foam cells				1			2
Foam cells in intima	1	3					
Foamy deposits				1			
Thickening, irregular					1		
Medial calcification	2						
Atherosclerosis with foam cells in subendothelium				3			
Atherosclerosis, severe with calcification							2
Lungs							
Foam cells in vessels		3		2			
Hemorrhage	1	3				1	
Edema	1	2				2	2
Skin							
Foam cells in dermis	1	2		5			
Brain							
Perivascular cuffing	2	1			1		
Marrow							
Congestion/hyperplasia		1					

[1] 10 rabbits per sex in control group and 5 rabbits per sex in all other groups were examined. The numbers indicate the total incidences of abnormalities in each group.

From these and other data on weight gain, blood chemistry, and other pathological findings, Carson and coworkers (1966) concluded that all changes in rabbits are attributable to cholesterol and not siloxanes.

Gollan (1961) has studied the effect of both polydimethylsiloxane and polymethylphenylsiloxane on rabbits fed both stock diets and diets containing 20,000 ppm cholesterol. The cholesterol levels found in serum, liver and aorta are given in Table XIX.

Table XIX. Cholesterol levels (grams) in the serum, liver and aorta of rabbits fed specified diets. (Gollan, 1961)

	Serum			Liver			Aorta		
	Avg.	S.D.	No.	Avg.	S.D.	No.	Avg.	S.D.	No.
2% cholesterol	1.373	.454	36	2.497	.701	27	.276	.171	27
Idem + .5% DC200*	1.015	.334	6	1.867	1.022	5	.543	.342	5
" + 1% DC200	.689	.314	6	--	--	--	--	--	--
" + 2% DC200	2.084	.230	6	2.672	.515	6	.682	.366	6
" + 5% DC200	1.855	.763	6	2.123	1.207	6	.669	.653	6
" + .5% XF-10050†	.559	.240	6	2.786	1.160	3	.557	.554	3
" + 1% XF-10050	.412	.138	6	--	--	--	--	--	--
" + 2% XF-10050	.558	.124	12	5.497	1.995	6	.135	.027	6
" + 5% XF-10050	.481	.156	6	3.589	.782	5	.218	.029	5
Stock diet	.073	.019	30	.218	.044	17	.117	.030	23
Idem + 2% DC200	.090	.034	24	.175	.032	16	.112	.041	11
" + 2% XF-10050	.072	.013	18	.170	.029	10	.083	.048	10

* Polydimethylsiloxane. † Polymethylphenylsiloxane.

The polydimethylsiloxane did not effect the development of hypercholesteremia except at the highest dose level, while the polymethylphenylsiloxane prevented hypercholesteremia at all levels. The dimethyl compound did not alter liver cholesterol but the methylphenyl compound markedly increased liver cholesterol at the 20000 and 50000 ppm siloxane level. The reverse effect is seen in the aorta where the dimethyl increases and the methylphenyl at higher levels does not effect cholesterol level. In the aorta, cholesterol with polydimethylsiloxane

resulted in marked foam cells in the intima of the aorta. The mechanism of these biological effects was not determined (Gollan, 1961). However, previous studies indicate that the effect is not related to changes in blood surface tension (Gollan, 1959; Merrill and Gollan, 1958).

The effect of polymethylphenylsiloxane on serum and liver cholesterol parallels the activity of 2,6-cis-diphenylhexamethylcyclotetrasiloxane noted by LeVier and Jankowiak (1972). This cyclic tetrasiloxane when administered to rats at 100 mg/day x 7 days decreased serum cholesterol (19.5 ± 1.1 mg/100 ml in treated as compared to 38.8 ± 4.4 in controls) and slightly increased liver cholesterol (2.41 mg/100 g in treated, 2.16 mg/100 g in control).

The information currently available thus seems equivocal. The results of Cutting (1952) are in direct opposition to those of Carson and coworkers (1966). That the latter group uses a non-cholesterol control is commendable but does not alter the fact that if cholesterol was the sole cause of renal tubular damage, Cutting (1952) should have seen such damage in the cholesterol control. No such damage was noted. The work of Gollan (1959 and 1961) definitely indicates effects on cholesterol metabolism and/or absorption for both the dimethyl and the methylphenyl siloxanes. These effects, if better understood, might explain the bile deposits noted by Child and coworkers (1951) and may relate to the stimulation of the conversion in the liver of stored dietary cholesterol and mevalonate to bile acid by an excess of dietary cholesterol as noted by Bricker and coworkers (1974).

B. Inhalation

The commercially important siloxanes have extremely low vapor pressures; thus, under normal conditions, inhalation would not be a significant route of exposure. Treon and coworkers (1954) have exposed several mammalian species to siloxane mists - not vapors. The experimental conditions and mortality results are summarized in Table XX.

Table XX. Mortality of various mammals exposed to mists of polydimethylsiloxane (DC200), 100 cSt., and polymethylphenylsiloxane (DC701), 9.2 cSt. at 25°C for 7 hours/day x 10 days under the specified conditions (Treon et al., 1954).

Siloxane	Amount of Material Aspirated mg/min	Rate of Passage of Air Through Aspirator, (at Room Conditions) l/min	Supplementary Flow of Air Into Chamber l/min	Concentration Found in Chamber mg/l	Number of Fatalities/Number of Animals Exposed			
					Cats	Guinea Pigs	Rabbits	Rats
DC-200 (1)	43.5	24.1	0	0.36	-	0/2	0/1	1/4
DC-200	42.1	24.1	28.3	0.25	0/1	0/2	0/1	0/4
DC-701	67.4	17.8	0	0.52	0/1	0/2	0/2 (2)	0/4

(1) One dog in this experiment survived exposure.
(2) One rabbit was exposed only during the final 7 periods.

None of the surviving animals showed any signs of intoxication during or after exposure. Histopathological examination did reveal moderate degenerative changes in the livers of cats and guinea pigs and a general increase in pneumonitis in a exposed species (Treon et al., 1954). In the absence of specific information on control group histopathology, these effects can be only circumstantially associated with siloxane exposure.

Unlike the higher molecular weight polymers, hexamethyldisiloxane is relatively volatile and a saturated atmosphere (40,000 ppm) caused respiratory failure in guinea pigs after 15-20 minutes. At lower concentrations or in shorter periods of exposure, the toxic effects are greatly reduced or disappear (Rowe et al., 1948).

Although there is little indication that these siloxanes are toxic on inhalation, their antifoaming properties have been used with some success in treating experimentally induced pulmonary edema (Nickerson and Curry, 1955; Princiotto et al., 1952).

C. Dermal Administration

Similar to inhalation toxicity, the physical and chemical properties of the long chain polymeric siloxanes would seem to preclude a high degree of dermal toxicity because of their negligible degree of cutaneous absorption (Hecht, 1968). Rowe and coworkers (1948) applied various polydimethylsiloxanes (0.65-25,000 cSt.) and polymethylphenylsiloxanes (35 and 75 cSt.) to the ears and shaven abdomens of rabbits twenty times in a one month period without causing appreciable irritation. Treon and coworkers (1954) have also applied polydimethylsiloxanes (100 cSt.) and polymethylphenylsiloxanes (9.2 cSt. at 25°C) to both intact and abraded skin of rabbits at doses of 6.0 and 9.4 ml/kg. The compounds were applied to an area of shaved skin 6-7 inches wide completely encircling the trunk and held in place by a sleeve for 24 hours. Although no skin reaction was noted, the higher dosage level caused death in two of three rabbits with abraded skin exposed to the dimethyl fluid and one fatality in each of two groups of three rabbits (intact and abraded skin) exposed to the methylphenyl fluid. Pathological examination of fatally exposed rabbits revealed pulmonary focal hemorrhage and edema and similar degenerative lesions in the parenchyma of the kidneys, heart, and brain. Surviving rabbits showed no such changes (Treon et al., 1954). Thus the relationship between the noted pathology and siloxane exposure is by no means conclusively established. However, the results do indicate that, at relatively massive

doses, both compounds may be passed through abraded skin and the methyl phenyl fluid may be absorbed through intact skin with possibly harmful effects.

D. Ocular Tolerance

Rowe and coworkers (1948) have applied various dimethyl and methylphenyl fluids directly in the eyes of rabbits. The results, summarized in Table XXI, are similar to the transient conjunctivitis noted in man (see Section XI, B).

Table XXI: Eye irritation in rabbits after direct application of various liquid siloxanes (Rowe et al., 1948)

Material	Viscosity in cSt. at 25°C	Occurrence and Persistence of Irritation					
		Immediately	1 hr.	4 hr.	8 hr.	24 hr.	48 hr.
DC 200 Fluid*	0.65	+	0	0	0	0	0
DC 200 Fluid	2.0	0	0	0	0	0	0
DC 200 Fluid	50.0	0	+	+	+	0	0
DC 550 Fluid	75.0	0	0	+	+	0	0
DC 702 Fluid+	35.0	0	0	+	+	0	0
DC 200 Fluid+	350.0	0	+	+	+	0	0
DC 200 Fluid	12,500	0	+	+	+	+	0

* polydimethylsiloxanes + polymethylphenylsiloxanes

Roughly, the viscosity seems directly related to the duration of irritation but inversely related to the rapidity of onset. Similar results were noted for DC Antifoam A (Rowe et al., 1948).

Badinand (1952) has also evaluated the ocular tolerance to both direct and vapor administration of various siloxanes. The applications and results are summarized in Table XXII.

Table XXII. Ocular tolerance of guinea pigs to direct and vapor application of various liquid siloxanes (adapted from Badinand, 1952)

Siloxane	Application	Result
Hexamethyldisiloxane	Vapor: 80-100 mg/l, 30-40 min/day x 20 days	Very slight epithelial disarrangement
	Direct: 1-2 drops/day x 15 days.	Slight corneal opacity without vascularization after 15 days.
Octamethylcyclotetrasiloxane	Vapor: 80 mg/l, 30 min/day x 22 days	Very slight clouding in the central region of the cornea
	Direct: 1-2 drops/day x 10 days	Very slight epithelial disarrangement with little infiltration and without perifocal reaction.
Polydimethylsiloxane (50 cSt.)	Vapor: 8-10 mg/l, 20 min/day x 10 days	Profound corneal opacity with an instance of vascularization lasting for five months.
Polydimethylsiloxane (2,000 cSt.)	Direct: 20 days	Slight erosions with neither opacity nor vascularization.
Polydiethylsiloxane (cSt. not specified)	Direct: 10 days	Very slight erosion of the corneal epithelium with neither infiltration nor vascularization, lasting for ten days.

On topical administration to the eye, these compounds seem to induce a minimal response. More details on ocular tolerance are described in the following section under "Intravitreous Injections."

E. Tissue Response to Siloxane Injections

Most of the studies involving the injection of liquid siloxanes into non-human mammals have been stimulated by the various medical uses of these products (see Section XI-D). Such studies might be seen to have broader applicability to siloxane toxicology if the various injection sites are viewed as means of artificially crossing various membrane barriers to siloxane absorption. With this approach, emphasis will be placed on tissue response rather than the overall suitability of these compounds in tissue augmentation, retinal retachment, and other medical uses. Dow Corning (1973a) has compiled an extensive bibliography on tissue reactions to polydimethylsiloxane.

1. Subcutaneous Injections:

Hexamethyldisiloxane (0.65 cSt.), dodecamethylpentasiloxane (2.0 cSt.), various polydimethylsiloxanes (50, 350, and 12,500 cSt.) and polymethylphenylsiloxanes (35 and 75 cSt.) have been injected subcutaneously into rabbits at doses of 0.1 ml. No effects were noted except for marked irritation and necrosis at the injection site of hexamethyldisiloxane (Rowe et al., 1948). In mice, subcutaneous injections of 2.0 and/or 3.0 ml. polydimethylsiloxane (20, 100, and 1,000 cSt.) resulted in neith gross tissue reaction nor inflammatory or foreign body reactions, although cyst formations and fluid losses from injection sites were noted (Ben-Hur and Neuman, 1963 and 1965). Although Ben-Hur and Neuman (1963) also noted areas of malignant tumor formation in two of the thirty-six mice tested, these were probably spontaneous mammary adenocarcinomas not related to siloxane injection (Grasso et al., 1964). An injection of 7-8 ml. polydimethylsiloxane (350 cSt.) in mice

resulted in siloxane deposits in the spleen, liver, adrenals, pancreas, ovaries, abdominal lymph nodes, and kidneys but no apparent toxic effects attributable to this distribution were noted (Rees et al., 1967). Similarly, in injections of 1 ml polydimethylsiloxane (350 cSt.) to mice, phagocytes were noted to ingest siloxanes and accumulations were apparent near the adrenal glands but no inflammatory response or tumor formation was evident (Ben-Ilur et al., 1967). Subcutaneous injection of 10 ml. dimethylpolysiloxane into the abdominal area of an ape showed some indication of phagocytic histocytes and degenerative connective tissue in the stoma and some cavities presumably filled with siloxanes and lined by foreign body giant cells (Winer et al., 1964).

2. Intraperitoneal Injections

Intraperitoneal injections follow much the same pattern as subcutaneous injections. Rowe and coworkers (1948) injected the same fluids outlined under subcutaneous injection at doses of 0.1, 0.3, 1.0, 3.0, and 10.0 ml/kg. Again, only hexamethyldisiloxane - at the three higher doses - caused fatalities, considerable irritation, and extensive adhesions throughout the viscera. All other fluids caused only non-inflammatory foreign body reactions which did not result in any noticeable toxic effects. Rees and coworkers (1967) also injected intraperitoneally as well as subcutaneously, the intraperitoneal doses in mice being 1 ml. They noted that the siloxane distribution paralleled the reticuloendothelial system indicative of possible collecting and storing by that system. On injecting rats with 10 ml. dimethylpolysiloxane (350 cSt.), Brody and Frey (1968) noted the typical granulomas response seen in other studies and found that the injections did not assist in the healing of intestinal abrasions. Using the same

compound, however, Ballantyne and coworkers (1971) injected 2-3 or 16 ml. i.p. into rats and found that peritoneal adhesions were reduced probably by mechanical separation of the abraded intestines from the peritoneal tissue. Again, the siloxane fluid caused no inflammatory response.

3. Intravenous Injection

Antifoaming agents rather than unadulterated siloxanes have been tested for toxicity by intravenous injection. DC Antifoam A administered to dogs into the right jugular vein had an LD_{50} of 0.9-1.0 ml/kg. Death was characterized by massive obstruction of the pulmonary artery or branches. In fatal cases, the right ventricles evidenced extreme distention not noted in surviving animals. Arterial administration via the carotid artery gave a much smaller LD_{50} of 0.02 mg/kg. In such exposures, fatal cases showed necrosis due to impeded blood flow to the brain which was also seen to a lesser extent in some surviving animals (Reed and Kittle, 1959). Smith (1960) observed similar brain lesions in dogs subjected to extracorporeal circulation in which a siloxane/silica antifoam was used. These lesions could have resulted from emboli caused by either the silica, the siloxanes, or both. In a recent study, the polydimethylsiloxane component of an antifoaming agent was shown to be able to occlude small pulmonary vessels but not produce any tissue response (Gupta et al., 1972).

4. Intravitreous Injections

As indicated previously (Section XI-D-1), polydimethylsiloxane fluids have been injected intravitreously in man as a therapy for complicated forms of retinal detachments with mixed results. In attempts to better define the biological activity of these polymers in the eye, similar injections

have been made in various laboratory mammals. Polydimethylsiloxane fluids (DC 360 Medical, viscosities of 500, 1,000, and 2,000 cSt.) have been intravitreously injected into five rabbits (0.5 - 0.75 ml) and seventeen monkeys (1.25 - 1.5 ml) after withdrawing an equal amount of fluid vitreous. Initially, a clear siloxane bubble was noted in the vitreous which occasionally showed transient mild opacity. In two monkeys, the surface of the retina evidenced small bubbles. Microscopic examination at periods of one day to one year after injection reveal that the siloxane injections cause the ganglion cells and inner nerve fiber layer of the retina to swell and vacuolize. This resulted in irreversible cellular damage to and loss of the ganglion cells in the compressed inner layer as indicated by partial disappearance of the cytoplasm. Similar damage was seen in receptor cells (Lee et al., 1969). In a subsequent study, one eye in each of eight monkeys was injected with a polydimethylsiloxane fluid (DC 360 Medical Grade, 2,000 cSt.) and subjected to histochemical and electron microscopic examination. After 2-3 hours, siloxane particles were noted in retinal tissue, particularly at the vitreoretinal interface. These particles seemed to attract free lipids and lipid accumulation surrounding siloxane particles was noted in the inner layer of the retina. Intercellular gaps a few microns in size were also noted in the superficial layers of the retina (Mukai et al., 1972). In a similar experiment, Labelle and Okun (1972) injected 0.4-0.6 ml. of polydimethylsiloxane (DC 360 Medical Grade, 2,000 cSt.) into the vitreous of fifteen rabbits. Histologic examinations were made after periods of one day to six months. The siloxane bubble remained clear and intact and no adverse effects were noted attributable to siloxane injection. Transient edema was noted in both siloxane

and control eyes after one week. Jodkaite (1971) also failed to note any inflammatory response from the injections of polydimethylsiloxane (400 cSt.) into the vitreous of rabbits although some tendency toward cataract formation was found.

5. Intra-articular Injection

Siloxane fluids have been used to lubricate arthritic joints in humans (Helal, 1968). However, such siloxanes, while not causing adverse effects, are not well retained in such spaces. Polydimethylsiloxane fluids (350 and 1,000 cSt.) have been injected into mobile and immobilized knee joints of rabbits. The siloxanes were gradually removed from all spaces and completely removed after three months. Similar injections into the knee joints of dead rabbits resulted in a much higher recovery of siloxanes. Histological examination revealed a mild granuloma-like inflammatory response similar to that noted in other injection sites. The difference in siloxane removal seen between living and dead rabbits seems to indicate that these compounds may be actively transported (Donahue et al., 1971). Von Luedinghausen and coworkers (1972) also noted considerable absorption of polydimethylsiloxane from the knee joints of rabbits but no inflammatory response was seen after the injection of one milliliter. Murray (1972) found that polydimethylsiloxane fluid (200 cSt.) will leave the synovial cavity of rabbits one week after a one milliliter injection either by leakage or phagocytosis and result in mild transitory inflammation.

6. Other Injections

Siloxanes have been injected at various other sites with tissue responses similar to those described above. Rowe and coworkers (1948), using

the same siloxanes described under subcutaneous injections, injected 0.1 ml intradermally in the back of a rabbit. As in the other sites, only hexamethyldisiloxane caused inflammation, edema, and necrosis. The other siloxanes formed blebs which disappeared after a few days. Autopsy revealed no organ damage on gross examination. Polydimethylsiloxane (DC 360 Medical Fluid, 12,500 cSt.) has been injected into the cisterna magna of rats and the spinal canals of rabbits and monkeys with no adverse effects attributable to siloxane injection (Hine et al., 1969). Imre and Pal (1968) have been able to induce avascular edema of the cornea by the injection of polydimethylsiloxane (DC 200, 350 cSt.) into the anterior chamber of the eye of rabbits similar to that seen by the introduction of vitreous. Tusa and Avila (1972) have injected polydimethylsiloxane intramuscularly into rabbits as a vehicle for progesterone without noting adverse effects.

F. Sensitization

As indicated previously, polydimethylsiloxane fluids (DC 200; 20, 50, and 100 cSt.) do not cause sensitization on repeated insult patch tests to humans. Similar results were also found in rats (Barry, 1973). In guinea pigs injected with a 1:1 mixture of polydimethylsiloxane (DC 360 Medical Fluid, 350 cSt.) and complete Freund's adjuvant at doses of 0.5 ml in the heel pads and 1.0 ml. subcutaneously in the flank, no antigen/antibody sensitization could be stimulated. Although repeated injections are not common, no information currently available indicates that the commercially important siloxanes are sensitizing by any route (Hobbs, 1973).

G. Teratogenicity

Two extremely different types of siloxanes have been tested for teratogenicity: a commercially available polydimethylsiloxane and an equilibrated copolymer of mixed cyclosiloxanes containing phenyl groups no longer commercially available.

A polydimethylsiloxane fluid (DC 360 Medical Fluid, 350 cSt.) has been tested for teratogenicity in rats and rabbits. The siloxane was administered subcutaneously at levels of 20, 200, and 1000 mg/kg/day to pregnant rabbits from day 6 to 18 and to pregnant rats from day 6 to 16. Control animals were injected with sesame oil, 1000 mg/kg. All litters were delivered by Caesarean section in rats (day 20) and rabbits (day 29). Summaries of results indicating some deviation from the control groups in rats and rabbits are given in Tables XXIII and XXIV, respectively.

Table XXIII. Results of teratogenic testing in rats injected with polydimethylsiloxane (Adapted from Food and Drug Research Laboratories, Inc., 1967).

Parameter	Polydimethylsiloxane, mg/kg			
	Control	20	200	1000
Total Number of Fetuses (all alive)	104	120	130	97
Implant sites (mean/liter)	10.0	9.2	9.0	8.7
Fetuses alive (mean/liter)	10.0	8.7	8.8	8.4
Pups with sternebrae not fully developed (per cent)	27	17.5	31	40
Bipartite sternebrae (per cent)	7.7	21.6	12.3	26.2

Table XXIV. Results of teratogenic testing in Rabbits with polydimethylsiloxane (adapted from Food and Drug Research Laboratories, Inc., 1967).

Parameter	Polydimethylsiloxane, mg/kg			
	Control	20	200	1000
*Total Number of Fetuses:				
alive	96 (63)	69 (48)	60 (33)	96 (46)
dead	0 (1)	6 (6)	10 (0)	12 (6)
Live Pups.litter	8.7	5.7	7.5	7.0
Implant sites (mean/liter)	8.8	6.7	9.9	8.2
Pups with sternebrae not fully developed (per cent):				
alive	6	8	3	15
*dead	0	83	-	100
Bipartite sternebrae (per cent)	0	0	3	2

* Number of animals examined for skeletal findings given in parentheses.

Although these results indicate a greater incidence of adverse effects in the siloxane groups, these findings are of questionable significance and do not clearly indicate teratogenicity (Food and Drug Research Laboratories, Inc., 1967).

Palazzolo and coworkers (1972) have evaluated the teratogenic potential in rabbits of an equilibrated copolymer of mixed cyclosiloxane with the formula $(PhMeSiO)_x(Me_2SiO)_y$ where $x \geq 1$ and $x + y = 3$ to 8. The dosages, routes of administration, and results are summarized in Table XXV.

Table XXV. Rabbit Teratogenic Study with Cyclic $(PhMeSiO)_x(Me_2SiO)_y$ (Palazzolo et al., 1972).

Group[a]	Test material	Route of administration	Dose (mg/kg)	Pregnant does	Implantation sites	Resorption sites	Does showing resorptions	Normal young		Abnormal young		24-hour viability[b] index
								Alive	Dead	Alive	Dead	
C	None	—	—	15	120	6	4	105	8	1	0	92.50
TC-I	Sesame oil	D[c]	200	15	110	14	8	91	3	1	1	93.80
TC-II	Sesame oil	ac	20	15	111	11	5	98	2	0	0	98.87
TC-III	Sesame oil	ac	200	15	112	14	5	92	6	0	0	93.84
TC-IV	Sesame oil	ac	1000	15	109	27	9	74	9	0	0	90.54
T-I	Phenyl	D	200	15	109	6	6	83	5	7	2	89.47
T-II	Phenyl	ac	20	15	117	11	7	96	6	2	0	92.63
T-III	Phenyl	ac	200	15	93	23	9	62	9	6	2	82.17
T-IV	Phenyl	ac	1000	15	77	33	11	37	7	0	0	84.78
T-V	Phenyl	D	50	10	70	6	3	64	0	0	0	93.00
T-VI	Phenyl	D	500	10	42	42	10	—	—	—	—	—

[a] C = control; TC = treated control group; T = test group.

[b] $\frac{\text{No. of viable young at 24 hr}}{\text{No. of viable young at birth}} \times 100$.

[c] D = dermal.

Palazzolo and coworkers (1972) indicate that the abnormality rate noted in the test group approaches "the upper limit of that expected for control rabbits of the same strain" and do not consider these compounds to be "specifically" teratogenic. However, 6 of the 8 abnormalities in T-3 and 2 of the 9 in T-1 were clubbing of the extremities. In addition, 2 of the 9 abnormalities in T-1 were partial acranius. The remaining abnormalities noted were umbilical hernias. LeFevre and coworkers (1972) fed pregnant rats the same mixture at levels of 200 mg/kg/day. In rats fed from days 1o-21, female - but not male - offspring had urogenital malformations resulting in inability to control urine flow. A specific siloxane from this class, monophenylheptamethylcyclotetrasiloxane, at doses up to 220 mg/kg/day did not produce this malformation in rat offspring.

H. Mutagenicity

No detailed study on silicone mutagenicity was encountered. Hobbs (1973) reports of a study indicating that a polydimethylsiloxane fluid is not mutagenic in albino mice. Drosophila has recently been the subject of a pilot study of the mutagenic activity of some organosilicones (Bennett, 1973), but the results have not been screened for this report.

I. Carcinogenicity

Frazer (1970) examined tumor induction in mice on diets of 0.25% and 2.5% polydimethylsiloxane (1000 cSt.) over an 80 week period as well as in mice injected subcutaneously in the left flank with 0.2 ml of this compound. Control groups consisted of those fed non-siloxane diets and mice injected with 0.2 ml. liquid paraffin. Tumor frequency was not greater in experimental groups than in controls. In the many other previously cited feeding studies, no evidence for tumor induction was noted. Thus, on oral administration, the siloxanes do not seem to be carcinogenic.

The polydimethylsiloxanes, however, will absorb various steroids such as testosterone, progesterone, cholesterol, and to a much lesser extent estradiol and esterone. Thus, siloxane injections could result in local hormone imbalances which might be conducive to tumor induction (Bischoff, 1969). Bryson (1969) tested a polydimethylsiloxane fluid (DC 360 Medical, 350 cSt.) for tumor induction in female rats as well as male and female mice. As summarized in Table XXVI, these animals demonstrated positive pathological findings not seen in controls unless otherwise indicated.

Table XXVI. Positive pathological findings in mice and rats injected with polydimethylsiloxane (Bryson, 1969)

Animal (number)	Rats, female (34)	Mice, male (22)	Mice, female (22)
Initial Dye	2 months	3 months	3 months
Dosage/Route	1.0 ml., i.p.	0.4 ml. s.c.	0.4 ml. i.p.
Exposure Period	17 months	20 months	18 months
Pathological Findings (number)	reticulum cell sarcomas (8)* local adeno-carcinoma (1)	heterotopic bone formation (1) fibrosarcoma (1) neurofibroma (1) diffuse lymphoma(1) ulcerating benign hyperplasia of the skin (1)	malignant histiocytic proliferation of the liver (1) fibrosarcoma (1) extramedullary hematopoiesis of the liver (2) fatty liver (1) lipogranuloma (1) fatty infiltration of lymph nodes (1) local necrosis with focal calcification (1) clear walled siloxane cysts (1)

* One in control group.

In those mice and rats in which tumors or other pathological results are not noted, the response was similar to the cyst formations and granulomatous responses noted in other injections studied (Bischoff et al., 1972).

Rees and coworkers (1965) found no evidence of malignant tumor formation in mice after subdermal or intradermal injections of polydimethylsiloxane in 45 rats over a 6 week to 12 month period. Subsequent investigations by the same group have failed to indicate that injected siloxanes are carcinogenic (Rees et al., 1970).

J. Behavioral Effects

An equilibrated copolymer of mixed cyclosiloxanes with the formula $(PhMeSiO)_x(Me_2SiO)_y$ - where $x \geq 1$ and $x + y = 3$ to 8 - has recently been shown to produce pronounced effects on the sexual physiology of various non-human mammals. This mixture, which will be referred to as PMxMMy, had previously been used in the cosmetic industry but has since been withdrawn from the market (Olson, 1972). The teratogenic effects of this polymeric mixture have been discussed in Section XII, G (p. 82).

This class of compounds has an androgen-depressant activity on male mammals. Palazzolo and coworkers (1972) have found that PMxMMy produced marked testicular atrophy and spermatogenic depression both on oral (200 mg/kg per day x 28 days) and dermal (5 mg/kg per day x 20 days) administrations to rabbits. These effects were reversible after exposure was terminated. Similar effects were noted in two species of male monkeys after oral but not dermal administration. Stumptail monkeys (Macaca arctoides) receiving 2000 mg/kg/day x 90 days developed progressively decreasing sperm counts after 3 weeks of dosing. After the 10th week of dosing, sperm samples could no longer be collected. Sperm production did not return to normal until 70 weeks after dosing was discontinued. Stumptail monkeys receiving 50 mg/kg/day x 90 days were apparently not affected. Rhesus monkeys (Mucaca mulata), however, were much more susceptible. Testicular atrophy with aspermatogenesis was produced after 8 weeks in two of three monkeys receiving 50 mg/kg/day and after 10 weeks in all three monkeys receiving 2000 mg/kg/day. Unlike the rabbits and stumptail monkeys, the rhesus monkeys did not recover from this condition during the investigation.

The androgen-depressant activity of a series of substituted siloxanes which might comprise the PMxMMy polymeric mixture has been examined by Bennett and coworkers (1972) using male mice, rats, and rabbits. Dose-response data on the effect of these siloxanes on rat seminal fluids, seminal vesicle, and prostate are given in Table XXVII. In this study, mice were less sensitive and rabbits more sensitive than rats.

Table XXVII. Oral Potency Comparison of Selected Phenyl-Substituted Siloxanes on Rat Seminal Fluid, Seminal Vesicle and Prostate[a] (Bennett et al., 1972)

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Compound	Daily dose (mg/kg)											
	100			33			10			3		
Disiloxanes: $R_3Si\text{-}O\text{-}SiR_3$												
$PhMe_2SiOSiMe_3$		0										
$PhMe_2SiOSiMe_2Ph$	82	89	91		0							
$Ph_2MeSiOSiMe_3$		0										
Trisiloxanes												
Linear: $R_3SiOSi(R_2)OSiR_3$												
$Me_3SiOSi(Ph)_2OSiMe_3$		0										
$Ph_2MeSiOSi(Me)_2OSiMe_3$	99	87	111		0							
$HOPhMeSiOSiPhMeOSiMePhOH$		0										
Cyclic:												
$[(PhMeSiO)(Me_2SiO)_2]$		0										
$[(PhMeSiO)_2(Me_2SiO)]$	61	92	79									
trans-$[(PhMeSiO)_3]$		0										
cis-$[(PhMeSiO)_3]$	53	91	78									
Tetrasiloxanes												
Linear: $R_3SiOSiR_2OSiR_2OSiR_3$												
$Me_3SiOSiPhMeOSiPhMeOSiMe_3$		0										
Cyclic:												
$[(Ph_2SiO)(Me_2SiO)_3]$		0										
$[(PhMeSiO)(Me_2SiO)_3]$	75	57	59	62	82	75	78	83	85		89	57
$[(PhMeSiO)(Me_2SiO)_3]$[d]	49	85	64				70	101	85		0	
$[(Ph_2SiO)(Me_2SiO)_3]$		0										
$[9PhMeSiO)_2(Me_2SiO)_2]$												
2,4-trans isomer	50	80	80					0				
2,4-cis isomer		0										
2,6-trans isomer		0										
2,6-cis isomer		0					41	71	61	57	80	65
$[(PhMeSiO)_2(Me_2SiO)]$		0										
$[(PhMeSiO)_4]$		0										

[a] The 3 numbers in sequence for any compound at any given dose denote the percent of control for seminal fluid, seminal vesicle, and prostate, respectively, after conversion to a ratio of fluid or organ weight to final body weight. "0" denotes no significant difference from control for the 3 response parameters, and therefore represents an inactive compound at this dose. Italicized numbers represent statistically significant differences from control where $p < 0.05$. Ten rats were used at each dose. Dosing lasted 7 days; autopsy was on day 8.

[b] 83% trans, 17% cis. [c] Fluid lost. [d] Dose listed under 100 is actually 60 mg/kg.

As can be seen from Table XXVII, a number of phenyl substituted siloxanes cause statistically significant ($p \leq 0.05$) effects at a dosing schedule of 100 mg/kg/day x 7 days. Two of the cyclic tetrasiloxanes are active at a one hundred fold lower concentration. Further, these two siloxanes were found to be more potent when administered orally as opposed to subcutaneous or intraperitoneal injections. In oral administration to rabbits, the effects of $[(PhMeSiO)(Me_2SiO)_3]$ on seminal vesicle and testes weight were shown to correspond with a decrease in plasma testosterone.

LeVier and Jankowiak (1972a) have attempted to characterize in greater detail the mechanism of action of the most active siloxane, 2,6-cis-diphenylhexamethylcyclotetrasiloxane - 2,6-cis$[(PhMeSiO)_2(Me_2SiO)_2]$ of Table XXVII. As with $[(PhMeSiO)(Me_2SiO)_3]$, 2,6-cis$[(PhMeSiO)_2(MeSiO)_2]$ caused a decrease in plasma testosterone. Either testosterone propionate or a combination of follicle-stimulating hormone, luteinizing hormone, and prolactin blocked the effect of this cyclic siloxane, thus indicating that the siloxane does not directly inactivate gonadotropins nor compete with them at receptor sites. However, the investigators were not able to determine if the siloxane directly or indirectly inhibited gonadotropin synthesis or release. Both of these active cyclic tetrasiloxanes were found to shorten hexobarbital sleep time in mice, indicating liver microsomal enzyme induction.

The androgen-depressant activity of these low molecular weight siloxanes in male mammals has been shown to correspond with a positive estrogenic activity in female mammals. LeFevre and coworkers (1972) noted that PMxMMy arrested the estrus cycle of mature female rats when administered orally at 100 mg/kg/day x 30 days. Rats on the first day of estrus went into metestrus for a few days

and then remained in diestrus. A normal estrus cycle did not develop until 2-3 weeks after exposure was terminated.

Similar to the study by Bennett and coworkers (1972) on male mammals, Hayden and Barlow (1972) determined the estrogenic potency of a series of substituted siloxanes on female mammals. The criterion for positive activity was the effect of a three day dosing of the various siloxanes on the uterine weights of ovarectomized immature female rats. The relative activities thus determined are summarized in Table XXVIII.

Table XXVIII. Comparative Relative Activities of 32 Organosiloxane Compounds Based on Effects on the Ovariectomized Immature Female Rat Uterus Following Oral Administration [Hayden and Barlow, 1972]; reprinted by permission. Copyright 1972, Academic Press

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Compound	Relative activity*
A. *Substituted siloxanes*	
Disiloxanes	
Phenyl substituted	
$PhMe_2SiOSiMe_3$	0
$PhMe_2SiOSiMe_2H$	0
$PhMe_2SiOSiMe_2Ph$	+2
$PhVinylMeSiOSiMe_3$	+1
$Ph_2MeSiOSiMe_3$	0
$(PhCH(CH_3)CH_3)Me_2SiOSiMe_3$	+1
Trisiloxanes	
Phenyl substituted	
Linear	
$Me_3SiOSiPhOHOSiMe_3$	0
$Me_3SiOSiPhHOSiMe_3$	+1
$Me_3SiOSiPh_2OSiMe_3$	+1
Cyclic	
$[(PhMeSiO)(Me_2SiO)_2]$	+2
$[(PhMeSiO)_2(Me_2SiO)]$	+3
2,4-*trans*-$[(PhMeSiO)_2(Me_2SiO)]$	+3
2,4-*cis*-$[(PhMeSiO)_2(Me_2SiO)]$	0
cis-$[(PhMeSiO)_3]$	+1
trans-$[(PhMeSiO)_3]$	+1
Tetrasiloxanes	
Cyclic	
$[(PhMeSiO)(Me_2SiO)_3]$	+4
[(*o*-tolylMeSiO)$(Me_2SiO)_3$]	+3
$[(HMeSiO)(Me_2SiO)_3]$	0 – +1
$[(VinylMeSiO)(Me_2SiO)_3]$	0 – +1
[(*n*-PrMeSiO)$(Me_2SiO)_3$]	0 – +1
$[(PhMeSiO)_4]$	+1
$[(Me_2SiO)_4]$	+1
$[(PhMeSiO)_2(Me_2SiO)_2]$ (racemic mixture)	+4
2,4-*cis*-$[(PhMeSiO)_2(Me_2SiO)_2]$	+1
2,6-*trans*-$[(PhMeSiO)_2(Me_2SiO)_2]$	+3
2,6-*cis*-$[(PhMeSiO)_2(Me_2SiO)_2]$	+4
$[(PhHSiO)(Me_2SiO)_3]$	+3
$[(Ph_2SiO)(Me_2SiO)_3]$	+1
$[(PhOHSiO)(Me_2SiO)_3]$	+1
B. *Miscellaneous*	
$OHMe_2SiPhSiMe_2OH$	0
$PhMe[SiCH_2CH_2SiMePhO]$	+3
$[(Me_2SiNH)(Me_2SiO)_3]$	+1
$(Me_2SiO)_3SiPh$	0

* Code: 0 = No effect; 1 = statistically nonsignificant increase < 20%; +2 = statistically significant increase at 0.05 level of significance; +3 = statistically significant increase at 0.01 level of significance; +4 = increase equal to or greater than estrogen treated controls

As with the androgen-depressant activity in males, the two cyclic tetrasiloxanes [$(PhMeSiO)(Me_2SiO)_3$] and 2,6-cis-[$(PhMeSiO)_2(Me_2SiO)_2$] are the most potent. Dose-response data on various tri- and tetrasiloxanes summarized in Table XXIX give a more concrete indication of relative potency.

Table XXIX: Effect of Selected Cyclotrisiloxanes and Cyclotetrasiloxanes on the Uterine Weight of Ovarectomized Female Rats Following Three-Day Oral Administration (Hayden and Barlow, 1972)

	Mean uterine wt. (mg/100 g body wt. ± SE)			
Castrate control	40.3 ± 5.9			
Positive control(0.1 μg estradiol benzoate)[a]	182.9 ± 10.4[c]			
	Dose of test compound[b]			
	10.0 mg/kg	1.0 mg/kg	0.1 mg/kg	0.01 mg/kg
$[(PhMeSiO)(Me_2SiO)_2]$	33.3 ± 1.0	35.5 ± 1.2	38.1 ± 1.2	34.7 ± 0.7
2,4-trans-$[(PhMeSiO)_2(Me_2SiO)]$	99.9 ± 2.2[c]	38.5 ± 0.5	37.5 ± 1.4	40.3 ± 1.9
2,4-cis-$[(PhMeSiO)_2(Me_2SiO)]$	35.0 ± 1.2	38.7 ± 2.2	44.5 ± 5.4	30.2 ± 1.3
$[(PhMeSiO)(Me_2SiO)_3]$	73.4 ± 2.3[c]	41.7 ± 2.1	39.8 ± 2.5	35.7 ± 2.3
2,6-cis-$[(PhMeSiO)_2(Me_2SiO)_2]$	173.6 ± 13.9[c]	211.3 ± 21.3[c]	82.5 ± 3.8[c]	48.9 ± 4.9
2,6-trans-$[(PhMeSiO)_2(Me_2SiO)_2]$	78.7 ± 4.0[c]	37.8 ± 2.0	39.2 ± 3.8	45.0 ± 6.4

[a] Total dose/animal/day.

[b] 6 animals/dose/compound.

[c] $p < 0.01$.

From this data, it is evident that 2,6-cis-[$(PhMeSiO)_2(Me_2SiO)_2$] is one hundred times more potent than either the trans isomer or [$(PhMeSiO)(Me_2SiO)_3$]. As in the studies on male mammals, the siloxanes were more potent when administered orally than when given by injection (Hayden and Barlow, 1972). In a subsequent study, it was found that the above cis-isomer administered to rats at 0.33 mg/kg/day on days 1-5 of gestation acts like a 0.05 mg/kg dose of diethylstilbestrol in effecting ova destruction in the uterus and more rapid passage of the ova to the uterus (LeVier and Jankowiak, 1972b).

The environmental significance of these findings is uncertain. The hormonally active compounds are no longer directly available commercially. Other polysiloxane fluids that are more widely used do not demonstrate any similar activity (Hobbs et al., 1972). However, the recent work of Ingebrightson (1975) on the breakdown of polydimethylsiloxane in soil suggests the possibility that polymethylphenylsiloxane might also break down and perhaps generate estrogenic low molecular weight siloxanes.

K. Possible Synergism

There is presently no indication that any of the siloxanes have synergistic effects.

XIII. TOXICITY TO LOWER ANIMALS

Toxicity studies encountered on non-mammals have concentrated primarily on various antifoams in an aquatic environment.

Fish seem quite tolerant to relatively high concentrations of silicone. SAG-10, a polydimethylsiloxane oil and silica emulsion, and SAG-350, a polydimethylsiloxane-oxyalkylene, both of Union Carbide, have no toxic effects on the flathead minnow in concentrations up to 2,000 mg/l over a four day exposure period (Spacie, 1972). Similarly, 1% DC Antifoam C (0.3% DC200), another polydimethylsiloxane, has no toxic effects on rainbow trout or bluegill sunfish over a four day exposure period (Barry, 1973).

Daphnia, however, have shown much more pronounced toxic response (See Table XXX).

Table XXX: Daphnia Mortality in Static Exposure to Siloxane Emulsions (Spacie, 1972)

A: Daphnia Mortality (%) in SAG 10 Solutions

	Concentration - mg/l						
Hours	0	1	10	100	500	1,000	2,000
24	0	0	20	10	40	30	60
48	0	20	20	10	40	50	100
96	0	30	40	40	50	100	100

B: Daphnia Mortality (%) in SAG 530 Solutions

	Concentration - mg/l						
Hours	0	1	10	100	500	1,000	2,000
24	0	0	0	0	10	10	40
48	0	0	0	0	10	30	60
96	10	0	10	10	20	80	100

The 96 hour LC_{50} of 500 mg/l SAG-10 and 500-1,000 mg/l SAG-530 might seem to indicate that these compounds are relatively non-toxic. However, LC_{50}'s are not absolute indicators of toxicity. Note that after 96 hours a 30% Daphnia mortality is achieved at 1 mg/l SAG-10, approximately 1 ppm. Needless to say, a 30% mortality of this important food source in aquatic systems would create considerable environmental stress. Thus, while this experiment was meant only as a preliminary evaluation and not as a definitive study, Spacie's conclusion that further studies are not required because of the high LC_{50}s is questionable.

Rausina (1974) has recently completed 48 hour static and dynamic exposures of Daphnia magna to a 30% polydimethylsiloxane emusion. Twenty daphnia were used in each group. The results are given in Table XXXI.

Table XXXI: Daphnia Magna Mortality (%) in Static and Dynamic Exposures to a 30% Polydimethylsiloxane Emulsion (Rausina, 1974)

Concentration (ppm): Emulsion (Siloxane)

Hours	0	1.0 (0.3)*	10 (3)*	62.5 (18.8)	100 (30)*	250 (75)	500 (150)	1,000 (300)
1-6	0; 0*	0	0	5	5	5	40	25; 15*
24	0; 10*	5	5	5	15	15	50	70; 60*
48	5; 10*	15	5	10	20	40	75	100; 85*

* static, all other figures indicate dynamic study.

Just as Spacie's study, because of limited number of specimens used and the short period of exposure, is no cause for alarm, so Rausina's study is no indication of aquatic innocuity. Both studies show similar mortality

in static exposures to 1 ppm emulsion for 48 hours - i.e., 20% in Spacie's and 15% in Rausina's. This is not particularly significant because a clear dose-response relationship is not established in these small groups until the concentrations reach about 100 ppm or until the exposure period is lengthened. The only thing indicated by either of these screening experiments is that the siloxane emulsions exert an adverse effect on Daphnia after a couple of days at environmentally improbable concentrations. The siloxanes themselves are, of course, not definitely implicated. Subsequent experiments using control, siloxane emulsion, and emulsifying agents without siloxane exposures may well prove the siloxanes to be without significant effect. Similarly, experiments outlined above reveal nothing about the effects of long term low level exposure. The death of a few Daphnia out of a group of 10 or 20 over a 2-3 day period may well be unrelated to exposure. However, even if the short-term lower limit of any aquatic biological activity is assumed to be 100 ppm siloxane, this is still the lowest level of biological activity thus far demonstrated. In that the aquatic environment may be a major site of siloxane disposal and distribution, further studies including population dynamics over periods of months may be indicated. Taylor (1973), in discussing the potential pollution of the marine environment by siloxanes and other organo-silicon compounds, did not apparently have access to the above cited studies and indicates that toxicity data on aquatic organisms are not available. However, he reasons that because "of the considerable body of evidence indicating the inertness of these compounds it seems safe to predict that the majority of the silicones are not toxic to marine life" (Taylor, 1973). The Daphnia studies suggest that this line of reasoning requires further verification.

No further toxicity studies were found. Unspecified silicones at 0.1 - 2.0% diet are reportedly fed to silkworms to increase body and cocoon weights, but no adverse effects are given (Hashimoto et al., 1972).

XIV. TOXICITY TO PLANTS

Parkinson (1970) has applied polydimethylsiloxanes (1,000 and 12,500 cSt.) to leaf surfaces of short grass, certain farm crops and trees as antitranspirants. While these applications have proven effective in conserving water, no toxic effects have been noted. A more detailed investigation of the antitranspirant effect of these silicones is in progress. Bennett (1973) indicates that no toxic effects have been noted thus far on 32 plant species.

XV. TOXICITY TO MICROORGANISMS

Various fluid polydimethylsiloxanes have been found to elicit no toxic response from the following bacteria: E. coli, P. aeruginosa, A. aerogenes, S. aureus, B. megaterium, and B. subtilis (Bennett, 1973). Similarly, unspecified polydimethylsiloxanes and polymethylphenylsiloxanes have shown no fungicidal properties (Sharp and Eggins, 1970).

XVI. CURRENT REGULATIONS

Polydimethylsiloxane (300-600 cSt. at 25°C) has been approved by the FDA as a food additive so long as the levels in prepared foods do not exceed 10 ppm except for gelatin desserts which may contain up to 16 ppm in prepared serving and milk which may not contain any trace of the siloxane (F.D.A., 1969).

Polydimethylsiloxanes (>100 cSt.) and/or polymethylphenylsiloxanes (not more than 2% cyclosiloxanes of up to 4 siloxy units) have been approved for use on metal surfaces which come in contact with food (F.D.A., 1972).

The Department of Transportation does not require a special label on siloxane products except when the formulation contains other active ingredients such as toluene (Union Carbide, 1973).

XVII. CONSENSUS AND SIMILAR STANDARDS - None encountered.

XVIII. Siloxane Fluids: Summary and Conclusions

The fluid siloxanes are a well-established group of commercial chemicals with considerable potential for further growth and development. Although a variety of fluid siloxanes are available as specialty products, the polydimethylsiloxanes are by far the most popular followed by the polymethylphenylsiloxanes. The remaining fluids are produced in relatively small amounts. Although exact production figures are difficult to estimate, the total quantity of siloxane produced for fluid applications in 1973 probably did not exceed 36 million pounds. These siloxanes are used in a great variety of applications including waxes, polishes, antifoams, lubricants, cosmetics, food additives, and textile finishings. Because the applications of these products may well become increasingly diversified, the growth rate may vary considerably but an estimate of ten percent per year seems reasonable for the immediate future.

Although these siloxanes are relatively expensive and most of their uses do not involve direct environmental release, many of the fluids are probably eventually released into the environment through disposal or use. However, because no monitoring data is available, the environmental distribution and fate of these compounds is a matter of speculation. Fairly good experimental data is available to demonstrate that the siloxanes are non-biodegradable, at least in test systems. However, a recent study has demonstrated that neutral soil will catalyze the hydrolysis and depolymerization of polydimethylsiloxanes (100 cSt.) at a relatively fast rate ($t_{\frac{1}{2}}$ = 10 days) to cyclic species and low molecular weight fragments terminated with the silanol group. This finding has considerable environmental significance since the

degradation products are more mobile in the environment, may be very persistent, could be bioaccumulated, and may be more toxic. Similar degradation processes are possible with other substituted siloxanes.

Consideration of the physical and chemical properties of the parent polysiloxanes and the breakdown products suggests that most of the siloxanes probably migrate to aquatic systems. Based on the assumption of aquatic accumulation, the highest probable concentration which would be found in the Great Lakes by 2023 would be .06 ppm if suspended in the water or 18 ppm if deposited in the bottom foot of silt. These figures probably represent maximum concentrations for most aquatic systems.

The potential for adverse environmental effects from such exposure is not readily defined. The high molecular polysiloxanes would seem to present a low degree of mammalian hazard at environmentally probable concentrations, even though the results of chronic feeding studies are equivocal. However, even assuming a negligible level of mammalian toxicity, the possibility of no adverse effects of these compounds on aquatic species is questionable. Although fish do not seem to be highly susceptible in four day exposures, such brief periods are of limited use in assessing the effects of long-term exposure. The two studies presented on Daphnia clearly indicate the need for further testing with larger groups over longer periods of time.

The possibility that high molecular weight polymethylphenylsiloxanes might be converted to low molecular weight estrogenic siloxanes is disturbing. The most potent of these siloxanes, 2,6-cis-diphenylhexamethylcyclotetrasiloxane has been shown to exert estrogenic effects in female rats at 0.1 mg/kg/day x 3 days and androgenic-depressant activity in male rats at

1.0 mg/kg/day x 7 days. Related siloxanes, while not as potent, nonetheless have similar effects. Thus, if long term exposure even to relatively low levels of such siloxanes were to occur, the potential effects on mammalian fecundity could be quite substantial and, therefore, would deserve considerable attention. However, it should be emphasized that the soil catalyzed breakdown of polymethylphenylsiloxanes to estrogenic substances has not been demonstrated experimentally. Nevertheless, the recent results with polydimethylsiloxanes make such analogous reactions not unlikely and the possibility of such reactions should be determined.

Further impediments to a sound evaluation of the potential environmental hazard posed by the fluid siloxanes center around the lack of monitoring data and the inadequate testing of aquatic invertebrate toxicity. Although present information in other areas does not indicate that high molecular weight siloxanes do or are likely to present an appreciable hazard, the above mentioned deficiencies should be corrected before new uses involving gross environmental exposure are initiated.

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